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(54) DERIVES DE 1,5-DIHYDRO-PYRAZOLO[3,4-D]-PYRIMIDINONE
(54) 1,5-DIHYDRO-PYRAZOLO[3,4-D]-PYRIMIDINONE DERIVATIVES

(57)

The invention relates to 1,5-dihydro-pyrazolo[3,4-d]-pyrimidinone derivatives which are produced by condensing the pyrimidone heterocycle on the appropriately substituted pyrazoles. Said compounds are suitable as active substances in medicaments, specially in medicaments used to treat cardiovascular and cerebrovascular diseases, peripheral vascular diseases and diseases of the urogenital tract.

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(54) DERIVES DE 1,5-DIHYDRO-PYRAZOLO[3,4-D]-
PYRIMIDINONE
(54) 1,5-DIHYDRO-PYRAZOLO[3,4-D]-PYRIMIDINONE
DERIVATIVES

(57) Des dérivés de 1,5-dihydro-pyrazolo[3,4-d]-pyrimidinone sont obtenus par condensation de l'hétérocycle de pyrimidinone sur les pyrazoles substitués de manière appropriée. Ces composés s'utilisent comme principes actifs dans des médicaments, notamment dans des médicaments employés dans le traitement de maladies cardio-vasculaires et cérébro-vasculaires, de maladies périphériques des vaisseaux, ainsi que dans des affections de l'appareil génito-urinaire.

(57) The invention relates to 1,5-dihydro-pyrazolo[3,4-d]-pyrimidinone derivatives which are produced by condensing the pyrimidone heterocycle on the appropriately substituted pyrazoles. Said compounds are suitable as active substances in medicaments, specially in medicaments used to treat cardiovascular and cerebrovascular diseases, peripheral vascular diseases and diseases of the urogenital tract.



PCT

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Internationales Büro

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INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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(54) Title: **1,5-DIHYDRO-PYRAZOLO[3,4-D]-PYRIMIDINONE DERIVATIVES**(54) Bezeichnung: **1,5-DIHYDRO-PYRAZOLO[3,4-D]-PYRIMIDINON-DERIVATE**

(57) Abstract

The invention relates to 1,5-dihydro-pyrazolo[3,4-d]-pyrimidinone derivatives which are produced by condensing the pyrimidone heterocycle on the appropriately substituted pyrazoles. Said compounds are suitable as active substances in medicaments, specially in medicaments used to treat cardiovascular and cerebrovascular diseases, peripheral vascular diseases and diseases of the urogenital tract.

(57) Zusammenfassung

Die 1,5-Dihydro-pyrazolo[3,4-d]-pyrimidinon-Derivate werden hergestellt, indem man an die entsprechend substituierten Pyrazole den Pyrimidoheterocyclus ankondensiert. Die Verbindungen eignen sich als Wirkstoffe in Arzneimitteln, insbesondere in Arzneimitteln zur Behandlung von kardiovaskulären und cerebrovaskulären Erkrankungen, peripheren Gefäßerkrankungen sowie Erkrankungen des Urogenitaltraktes.

Veröffentlicht

*Mit internationalem Recherchenbericht.**Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.*

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TEXT TRANSLATION

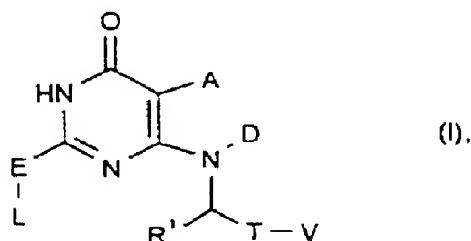
1,5-Dihydro-pyrazolo[3,4-d]-pyrimidinone derivatives

The present invention relates to 1,5-dihydro-pyrazolo[3,4-d]-pyrimidinone derivatives, to a process for their preparation, and to their use in medicaments, in particular for the treatment of cardiovascular and cerebrovascular diseases, diseases of the peripheral vessels, and diseases of the urogenital system.

Phosphodiesterases (PDEs) play an important role in the regulation of the intracellular cGMP and cAMP level. Amongst the phosphodiesterase isoenzyme groups PDE I to PDE V which have been described to date [Nomenclature of Beavo and Reifsnyder (cf. Beavo, J.A. and Reifsnyder, D.H.: Trends in Pharmacol. Sci 11, 150 - 155 (1990)], the Ca-calmodulin-activated PDE I, the cGMP-stimulateable PDE II and the cGMP-specific PDE V are essentially responsible for the cGMP metabolism. Due to the different distribution of these cGMP-metabolizing PDEs in the tissue, selective inhibitors should, depending on the distribution in the tissue of the isoenzyme in question, increase the c-GMP levels in the tissue in question. This may lead to a specific antiaggregatory, antispastic, vasodilatory and/or antiarrhythmic action.

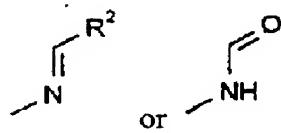
Moreover, US-5 294 612, US-4 211 731, US-3 211 732, WO 96/28448 and WO 96/28429 disclose 6-heterocyclyl-pyrazolo[3,4-d]pyrimidin-3-one and 6-substituted pyrazolo[3,4-d]pyrimidin-4-ones, which can be employed for hypertension, angina and heart diseases.

The present invention now relates to 1,5-dihydro-pyrazolo[3,4-b]-pyrimidone derivatives of the general formula (I)



in which

A and D together represent a radical of the formula



where

5

R^2 represents aryl which has 6 to 10 carbon atoms and which is optionally up to trisubstituted by identical or different substituents from the series consisting of nitro, cyano, hydroxyl, trifluoromethyl, halogen, carboxyl, or by straight-chain or branched acyl, alkoxy or alkoxy carbonyl, each of which has up to 6 carbon atoms or hydrogen, trifluoromethyl, cyano, carboxyl, or straight-chain or branched alkoxy or alkoxy carbonyl, each of which has up to 8 carbon atoms, or straight-chain or branched alkyl which has up to 8 carbon atoms and which is optionally substituted by hydroxyl,

10

15

R^1 represents straight-chain or branched acyl having up to 4 carbon atoms, or represents straight-chain or branched alkyl having up to 10 carbon atoms, optionally substituted by hydroxyl, azido or by a group of the formula $-NR^3R^4$ or $-OSO_2R^5$

20

where

R^3 and R^4 are identical or different and

25

represent hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, or

30

R^3 and R^4 together with the nitrogen atom form a 5 or 6-membered saturated heterocycle which can optionally contain a further hetero atom selected from the series consisting of S or O or a radical $-NR^6$

where

R^6 represent hydrogen or straight-chain or branched alkyl is up to 4 carbon atoms

and

5

R^5 represents phenyl or straight-chain or branched alkyl having up to 5 carbon atoms,

10

E represents a straight-chain or branched alkylene or alkenylene chain, each of which has up to 6 carbon atoms which are optionally substituted by hydroxyl, or represents the $C=O$ group,

15

L and V are identical or different and represent aryl having 6 to 10 carbon atoms or a 5- to 7-membered aromatic, optionally benzo-fused, heterocycle which has up to 3 hetero atoms from the series consisting of S, N and/or O which are optionally up to trisubstituted by identical or different substituents from the series consisting of halogen, hydroxyl, nitro, trifluoromethyl, carboxyl, straight-chain or branched alkyl, alkoxy or alkoxy carbonyl, each of which has up to 6 carbon atoms, or by a group of the formula $-(W)_a-NR^7R^8$

20

where

25

a is a number 0 or 1,

W is a radical of the formula $-CO$ or $-SO_2$,

30

R^7 and R^8 are identical or different and have the abovementioned meaning of R^3 and R^4 ,

35

and/or the cycles are optionally substituted by aryl having 6 to 10 carbon atoms or by a 5- to 7-membered aromatic, optionally benzo-fused, heterocycle having up to 3 hetero atoms from the series consisting of S, N and/or O, which, in turn, are optionally up to disubstituted by identical or different substituents from the series consisting of halogen, hydroxyl, nitro, carboxyl, trifluoromethyl or by straight-chain or branched alkyl, alkoxy or

alkoxycarbonyl, each of which has up to 5 carbon atoms, or by a group of the formula $-(W')_b-NR^9R^{10}$

where

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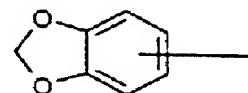
b has the abovementioned meaning of a and is identical to this meaning or different from it,

10 R^9 and R^{10} have the abovementioned meaning of R^3 and R^4 and are identical to this meaning or different from it,

W' has the abovementioned meaning of W and is identical to this meaning or different from it,

15

or



L represents a radical of the formula

or

20

V represents methyl,

T represents a radical of the formula $-CH_2-X-Y-$

25

where

X represents a bond or an oxygen or sulphur atom or the $-NH$ -group,

30

Y represents a straight-chain or branched alkylene chain having up to 9 carbon atoms,

and the tautomers and salts of these.

The substances according to the invention may also be present as salts. Preferred within the scope of the invention are physiologically acceptable salts.

Physiologically acceptable salts can be salts of the compounds according to the invention with inorganic or organic acids. Preferred are salts with inorganic acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonic acids such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, lactic acid, benzoic acid, or methanesulphonic acid, ethanesulphonic acid, phenylsulphonic acid, toluenesulphonic acid or naphthaline disulphonic acid.

Equally, physiologically acceptable salts may be metal salts or ammonium salts of the compounds according to the invention which have a free carboxyl group. Especially preferred examples are sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia, or organic amines such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine, ethylenediamine or 2-phenylethylamine.

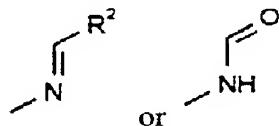
The compounds of the general formula (I) according to the invention can occur in various stereochemical forms which relate to each other either like image and mirror image (enantiomers) or which do not relate to each other like image and mirror image (diastereomers). The invention relates not only to the antipodes, but also to the racemic forms and the diastereomer mixtures. The racemic forms and the diastereomers can be separated in a known manner to give the stereoisomerically uniform constituents.

Within the scope of the invention, heterocycle generally represents a saturated or unsaturated 5- to 7-membered, preferably 5- to 6-membered, heterocycle which can contain up to 3 hetero atoms from the series consisting of S, N and/or O. Examples which may be mentioned are: pyridyl, thienyl, indonyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, morpholinyl or piperidyl. Pyridyl, thienyl, indolyl and furyl are preferred.

Preferred compounds of the general formula (I) are those

in which

A and D together represent a radical of the formula



5

where

10 R^2 represents phenyl which is optionally up to disubstituted by identical or different substituents from the series consisting of nitro, cyano, hydroxyl, trifluoromethyl, fluorine, chlorine, bromine, carboxyl or by straight-chain or branched acyl, alkoxy or alkoxy carbonyl, each of which has up to 5 carbon atoms,

or

15 hydrogen, trifluoromethyl, cyano, carboxyl, straight-chain or branched alkoxy or alkoxy carbonyl, each of which has up to 6 carbon atoms, or straight-chain or branched alkyl which has up to 6 carbon atoms and which is optionally substituted by hydroxyl,

20 R^1 represents straight-chain or branched acyl having up to 6 carbon atoms, or straight-chain or branched alkyl which has up to 8 carbon atoms and which is optionally substituted by hydroxyl, azido or by a group of the formula $-NR^3R^4$ or $O-SO_2-R^5$

25 in which

R^3 and R^4 are identical or different and represent

hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, or

30 R^3 and R^4 together with the nitrogen atom form a morpholinyl-piperidinyl or piperazinyl ring, the latter optionally being substituted via the nitrogen function by straight-chain or branched alkyl having up to 3 carbon atoms,

35

and

R^5 represents phenyl or straight-chain or branched alkyl having up to 4 carbon atoms,

5

E represents a straight-chain or branched alkylene or alkenylene chain, each of which has up to 5 carbon atoms and each of which is optionally substituted by hydroxyl, or
represents the C=O group,

10

L and V are identical or different and represent phenyl, naphthyl, pyridyl, thienyl, indolyl or furyl, each of which is up to trisubstituted by identical or different substituents from the series consisting of fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, nitro, carboxyl, straight-chain or branched alkyl, alkoxy or alkoxy carbonyl, each of which has up to 5 carbon atoms, or by a group of the formula $-(W)_aNR^7R^8$

15

in which

20

a represents a number 0 or 1,

W represents a radical of the formula -CO or -SO₂,

25

R^7 and R^8 are identical or different and have the abovementioned meaning of R^3 and R^4 ,

30

and/or the cycles are optionally substituted by naphthyl, phenyl, pyridyl, indolyl, thienyl or furyl, optionally by phenyl, naphthyl, pyridyl, thienyl, furyl, pyrryl or pyrimidyl, which, in turn, are optionally substituted by fluorine, chlorine, bromine, hydroxyl, nitro, carboxyl, trifluoromethyl or straight-chain or branched alkyl, alkoxy or alkoxy carbonyl, each of which has up to 3 carbon atoms, or by a group of the formula $-(W')_bNR^9R^{10}$

in which

35

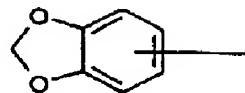
b has the abovementioned meaning of a and is identical to this meaning or different from it,

W' has the abovementioned meaning of W and is identical to this meaning or different from it,

5 R⁹ and R¹⁰ have the abovementioned meaning of R³ and R⁴,

or

L represents a radical of the formula



10

or

V represents methyl,

15 T represents a radical of the formula -CH₂-X-Y-

in which

X represents a bond or an oxygen or sulphur atom or the -NH- group,

20

Y represents a straight-chain or branched alkylene chain having up to 8 carbon atoms,

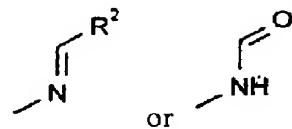
and the tautomers and salts of these.

25

Especially preferred are compounds of the general formula (I)

in which

30 A and D together represent a radical of the formula



in which

5 R^2 represents phenyl which is optionally up to disubstituted by identical or different substituents from the series consisting of nitro, cyano, hydroxyl, trifluoromethyl, fluorine, chlorine, bromine, carboxyl or by straight-chain or branched acyl, akyo or alkoxy carbonyl, each of which has up to 4 carbon atoms,
or
10 represents hydrogen, trifluoromethyl, cyano, carboxyl, straight-chain or branched alkoxy or alkoxy carbonyl, each of which has up to 5 carbon atoms, or straight-chain or branched alkyl which has up to 5 carbon atoms and which is optionally substituted by hydroxyl,

15 R^1 represents straight-chain or branched acyl having up to 5 carbon atoms,
or
represents straight-chain or branched alkyl which has up to 6 carbon atoms and which is optionally substituted by hydroxyl, azido or by a group of the formula $-NR^3R^4$ or $O-SO_2R^5$

20 in which

 R^3 and R^4 are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, or

25 R^3 and R^4 together with the nitrogen atom form a morpholinyl, piperdinyl or piperazinyl ring, the latter optionally being methyl-substituted via the nitrogen function,

30 and
 R^5 represents phenyl or straight-chain or branched alkyl having up to 3 carbon atoms,

35 E represents a straight-chain or branched alkylene or alkenylene chain, each of which has up to 5 carbon atoms which are optionally substituted by hydroxyl, or
represents the $C=O$ group,

5 L and V are identical or different and represent phenyl, naphthyl, furyl, thienyl, indolyl or pyridyl, each of which is optionally up to trisubstituted by identical or different substituents from the series consisting of fluorine, chlorine, bromine, hydroxyl, nitro, carboxyl, straight-chain or branched alkyl, alkoxy or alkoxy carbonyl, each of which has up to 4 carbon atoms, or by a group of the formula -(W)_aNR⁷R⁸

10 in which

a represents a number 0 or 1,

15 W represents a radical of the formula -CO or -SO₂,

20 R⁷ and R⁸ are identical or different and have the abovementioned meaning of R³ and R⁴,

25 and/or the cycles are optionally substituted by phenyl, pyridyl, thienyl or furyl, which, in turn, are optionally substituted by fluorine, chlorine, bromine, hydroxyl, nitro, carboxyl, trifluoromethyl or by straight-chain or branched alkyl, alkoxy or alkoxy carbonyl, each of which has up to 3 carbon atoms, or by a group of the formula -(W')_bNR⁹R¹⁰

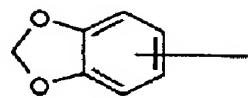
30 in which

25 b has the abovementioned meaning of a and is identical to this meaning or different from it,

30 W' has the abovementioned meaning of W and is identical to this meaning or different from it,

35 R⁹ and R¹⁰ have the abovementioned meaning of R³ and R⁴,

or



L represents a radical of the formula

or

5 V represents methyl,

T represents a radical of the formula -CH₂-X-Y-

in which

10

X represents a bond or an oxygen or sulphur atom or the -NH-group,

Y represents a straight-chain or branched alkylene chain having up to 6 carbon atoms,

15

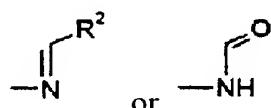
and the tautomers and salts of these.

Very especially preferred are compounds of the general formula (I) according to the invention

20

in which

A and D together represent a radical of the formula



25

in which

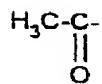
30

R² represents straight-chain or branched alkyl or alkoxy, which has up to 3 carbon atoms,

R¹ represents a straight-chain or branched alkyl having up to 3 carbon atoms

or

a radical of the formula



5 E represents a straight-chain or branched alkylene chain which has up to 3 carbon atoms and which is optionally substituted by hydroxyl,

10 T represents a radical of the formula $-\text{CH}_2\text{-X-Y-}$

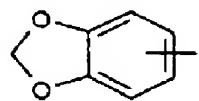
in which

10 X represents a bond and

15 Y represents a straight-chain or branched alkylene chain having up to 5 carbon atoms,

15 V represents methyl or phenyl,

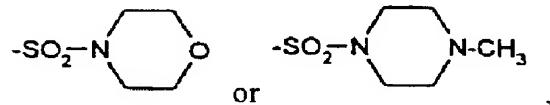
20 L represents a radical of the formula



20

or

25 phenyl which is optionally up to trisubstituted by identical or different substituents from the series consisting of fluorine, chlorine, bromine, pyridyl, straight-chain or branched alkyl or alkoxy carbonyl, each of which has up to 3 carbon atoms, amino or by a radical of the formula $-\text{SO}_2\text{-NHCH}_3$



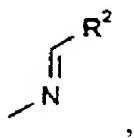
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and/or can be substituted by phenyl or by nitro-substituted phenyl,

and the tautomers and salts of these.

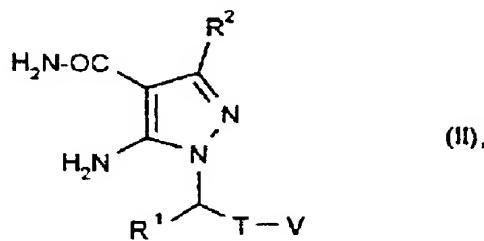
Moreover, a process for the preparation of the compounds of the general formula (I) according to the invention has been found, characterized in that

5 [A] in the event that A and D together represent the radical of the formula



compounds of the general formula (II)

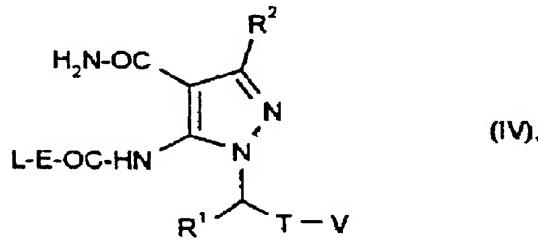
10



in which

15 R¹, R², T and V have the abovementioned meaning

are firstly converted into the compounds of the general formula (IV)



20

in which

E, L, T, V, R¹ and R² have the abovementioned meaning

by reacting them, in inert solvents and in the presence of a base, with compounds of the general formula (III)



5

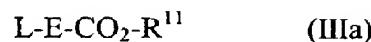
in which

E and L have the abovementioned meaning

10 and subsequently cyclizing the product with bases,

or

15 [B] compounds of the general formula (II) are reacted, with direct cyclization, with compounds of the general formula (IIIa)



in which

20

E and L have the abovementioned meaning

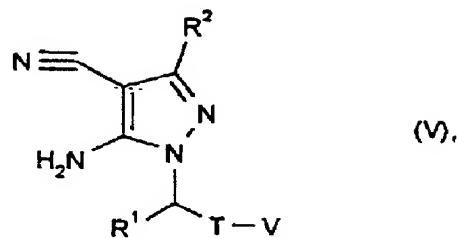
and

25 R^{11} represents methyl or ethyl,

and, in a second step, the product is cyclized in inert solvents and in the presence of a base,

30 or

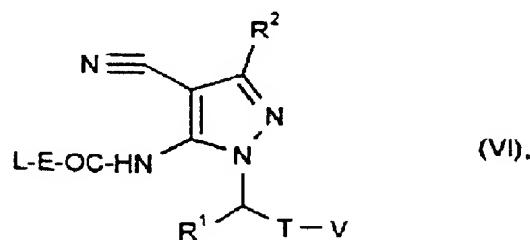
[C] compounds of the general formula (V)



in which

5 R¹, R², T and V have the abovementioned meaning

are first reacted with compounds of the general formula (III) in inert solvents and in the presence of a base to give the compounds of the general formula (VI)



10

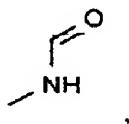
in which

R¹, R², E, L, T and V have the abovementioned meaning,

15 and, in a 2nd step, cyclizing the product in inert solvents and in the presence of a base and of an oxidant,

or

20 [D] in the event that A and D together represent the radical of the formula



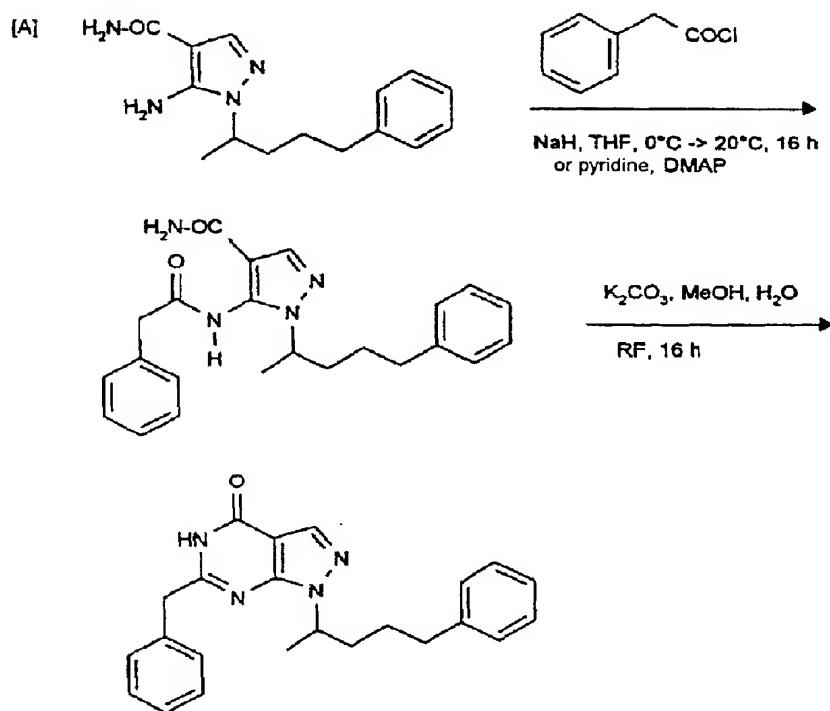
the corresponding compounds of the general formula (I) in which R² represents methoxy is reacted in the system sodium iodide/trimethylchlorosilane in inert solvents,

5 and, if appropriate, the substituents mentioned under R¹ are introduced or derivatized by subsequent reactions such as acylation, oxidation, substitution and/or reductions,

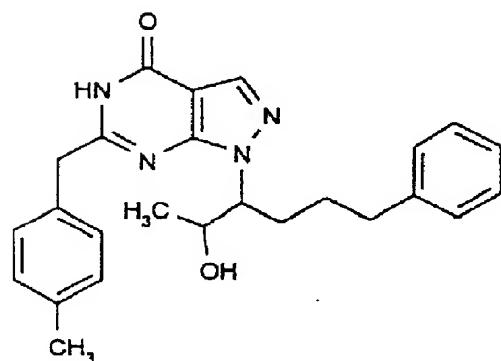
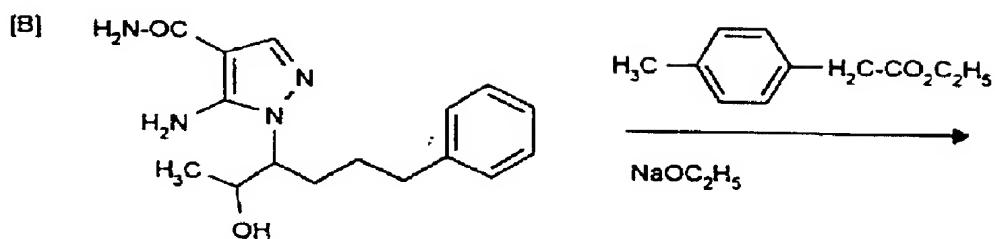
and, equally, the substituents mentioned above under L and V are introduced and/or varied by customary methods.

10

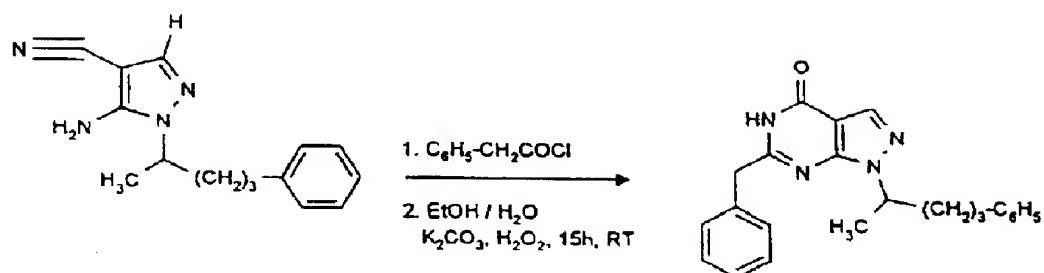
The process according to the invention can be illustrated by way of example with reference to the following formula scheme:



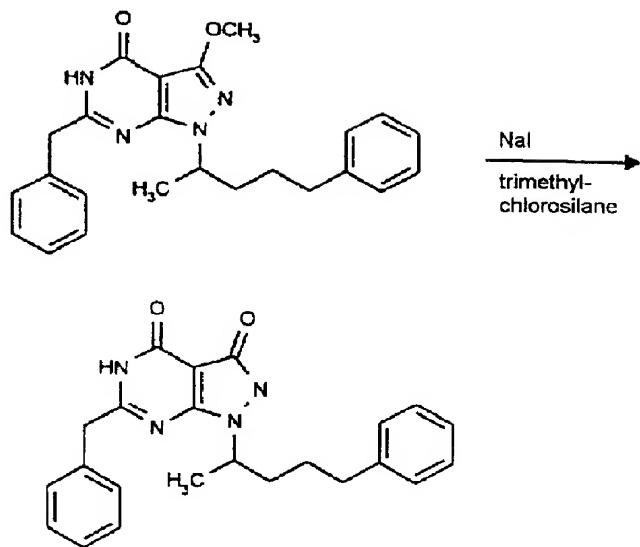
15



[C]



[D]



Suitable solvents for the first step of process [A] and process [C] are inert organic solvents which do not change under the reaction conditions. These preferably include ethers such as, for example, diethyl ether, dioxane, tetrahydrofuran or glycol dimethyl ether or toluene, hexamethylphosphoric triamide and pyridine. Naturally, solvent mixtures may be used. Especially preferred are tetrahydrofuran, toluene or pyridine.

Suitable bases are, in general, alkali metal hydrides or alkali metal alkoxides such as, for example, sodium hydride or potassium tert-butoxide, or cyclic amines such as, for example, piperidine, pyridine, dimethylaminopyridine or C₁-C₄-alkylamines such as, for example, triethylamine. Preferred are sodium hydride, pyridine and/or dimethylaminopyridine.

15 In general, the base is employed in an amount of 1 mol to 4 mol, preferably 1.2 mol to 3 mol, in each case per mole of the compounds of the general formula (II) and (V).

In general, the reaction temperature can be varied within a substantial range. In general, the process is carried out in a range of -20°C to 200°C, preferably 0°C to 100°C.

In one variant, the reaction is carried out in pyridine to which a catalytic amount of DMAP is added. If appropriate, toluene may also be added.

Suitable solvents for the cyclization reaction are the customary organic solvents. These preferably include alcohols such as methanol, ethanol, propanol, isopropanol, butanol or t-butanol, or ethers such as tetrahydrofuran or dioxane, or dimethylformamide or dimethyl sulphoxide. Alcohols such as methanol, ethanol, 5 propanol, isopropanol or t-butanol are especially preferably used. Mixtures of the above solvents may also be employed.

Bases which are suitable for the cyclization reaction are the customary inorganic bases. These preferably include alkali metal hydroxides or alkaline earth metal 10 hydroxides such as, for example, sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal carbonates such as sodium carbonate, potassium carbonate or sodium hydrogen carbonate, or alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide or potassium tert-butoxide. Potassium carbonate, sodium hydroxide and potassium tert-butoxide are 15 especially preferred.

When carrying out the cyclization reaction, the base is generally employed in an amount of 2 to 6 mol, preferably 3 to 5 mol, per mol of the compounds of the formula (IV).

20 Suitable oxidants for the cyclization reaction are, for example, hydrogen peroxide or sodium borate. Hydrogen peroxide is preferred.

25 In general, the cyclization reaction is carried out in a temperature range between 0°C and 160°C, preferably at the boiling point of the solvent in question.

In general, the cyclization reaction is carried out under atmospheric pressure. However, it is also possible to carry out the process under superatmospheric or subatmospheric pressure (for example in a range between 0.5 to 5 bar).

30 Suitable solvents for process [B] are the abovementioned alcohols, ethanol being preferred.

35 Suitable bases for process [B] are alkoxides such as, for example, sodium methoxide, sodium ethoxide, sodium isopropoxide or potassium tert-butoxide. Sodium ethoxide is preferred.

The base is employed in an amount of 2 to 8 mol, preferably 3 mol to 6 mol, in each case per mole of the compounds of the general formula (II).

5 The preferred solvent for process [D] is acetonitrile. In general, the process is carried out under reflux conditions and under atmospheric pressure.

Starting from the corresponding free hydroxyl compounds, the reaction with alkylsulphonyl chlorides is carried out in one of the abovementioned solvents and one of the bases, preferably with dichloromethane and triethylamine, in a temperature 10 range between -20°C to +20°C, preferably 0°C and atmospheric pressure.

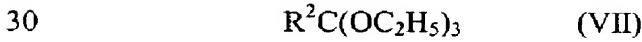
15 The azide radical is generally introduced by reacting the corresponding alkylsulphonyloxy-substituted compounds with sodium azide in one of the abovementioned solvents, preferably dimethylformamide, in a temperature range between 50°C and +120°C, preferably 100°C and atmospheric pressure.

Starting from the corresponding hydroxyl compounds, the ketones are prepared by known methods (Swern oxidation or Collins oxidation).

20 The substituents on the aromatic rings are varied by known methods.

The enantiomerically pure compounds can be obtained by customary methods, for example by chromatography of the racemic compounds of the general formula (I) on chiral phases, or by using chiral starting compounds.

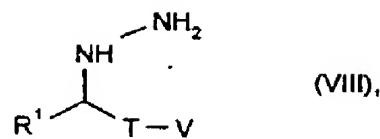
25 The compounds of the general formula (V) are new and can be prepared, for example, by reacting - in the event that $R^2 \neq OCH_3$ - malononitrile with compounds of the general formula (VII)



in which

R^2 has the abovementioned meaning

35 and, in a second step, with compounds of the general formula (VIII)



in which

5 R¹, T and V have the abovementioned meaning

in inert solvents,

and - in the event that R² = OCH₃ - reacting the compounds of the general formula
10 (VIII) directly with 1,1-dimethoxy-2,2-dicyano-ethylene.

Suitable solvents for the individual process steps are the customary organic solvents
which do not change under the reaction conditions. These preferably include alcohols
such as methanol, ethanol, propanol or isopropanol, or ethers such as diethyl ether,
15 dioxane, tetrahydrofuran, glycol dimethyl ether, or hydrocarbons such as benzene,
toluene, xylene, hexane, cyclohexane or mineral oil fractions, or
halogenohydrocarbons such as dichloromethane, trichloromethane,
tetrachloromethane, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl
acetate, dimethylformamide, hexamethylphosphoric triamide, acetonitrile, acetone,
20 dimethoxyethane or pyridine. Mixtures of the above solvents may also be used.
Especially preferred are acetonitrile in the event that R² ≠ OCH₃ and pyridine in the
event that R² = OCH₃.

In general, the process according to the invention is carried out in a temperature
25 range between 0°C and +180°C, preferably between +30°C and +150°C.

These process steps according to the invention are generally carried out at
atmospheric pressure. However, the process may also be carried out at
superatmospheric pressure or subatmospheric pressure (for example in a range
30 between 0.5 and 5 bar).

Most of the compounds of the general formula (IV) and (VI) are new and can be
prepared as described above.

The compounds of the general formula (III), (IIIa), (VII) and (VIII) are known per se or can be prepared by customary methods.

5 The compounds of the general formula (II) are new and can be prepared by reacting the compounds of the general formula (V) with one of the abovementioned oxidants, preferably hydrogen peroxide, in the presence of ammonia or dichloromethane, or with a phase transfer catalyst.

10 Some of the compounds of the general formula (V) are known or new or can be prepared by customary methods.

The compounds of the general formula (I) according to the invention have a valuable pharmacological spectrum of action which could not have been foreseen.

15 They inhibit either one or more of the c-GMP-metabolizing phosphodiesterases (PDE I, PDE II and PDE V). This leads to a differentiated increase in c-GMP. An increased c-GMP level can lead to an antithrombotic, vasodilatory and/or antiarrhythmic action. The differentiating action is determined, *inter alia*, by the distribution of the isoenzymes in the tissue.

20 Moreover, the compounds according to the invention promote the action of substances such as, for example, EDRF (endothelium derived relaxing factor) and ANP (atrial natriuretic peptide) which increase the cGMP level.

25 They can therefore be used in medicaments for treating cardiovascular diseases such as, for example, for treating hypertension, neuronal hypertension, stable and unstable angina, diseases of the peripheral and cardial blood vessels, of arrhythmias, for treating thromboembolic diseases and ischaemias such as myocardial infarction, stroke, transitory and ischaemic attacks, angina pectoris, peripheral circulation disorders, prevention of restenoses after thrombolytic therapy, percutaneous transluminal angioplasty (PTA), percutaneous transluminal coronary angioplasties (PTCA) and bypass. The relaxing effect on the smooth muscles makes them suitable for the treatment of diseases of the urogenital system such as prostatic hypertrophy, impotence and incontinence. Moreover, they can also be of importance for cerebral vascular diseases.

Phosphodiesterase (PDE) activity

The c-GMP-stimulatable PDE II, the c-GMP-inhibitible PDE III and the cAMP-specific PDE IV were isolated either from porcine or bovine heart myocard. The 5 Ca^{2+} -calmodulin-stimulatable PDE I was isolated from porcine aorta, porcine brain or, preferably, bovine aorta. The c-GMP-specific PDE V was obtained from porcine small intestine, porcine aorta, human platelets and, preferably, bovine aorta. They were purified by anion exchange chromatography on MonoQ^R Pharmacia following 10 essentially the method of M. Hoey and Miles D. Houslay, Biochemical Pharmacology, Vol. 40, 193-202 (1990) and C. Lugman et al. Biochemical Pharmacology Vol. 35 1743-1751 (1986).

The enzyme activity is determined in a test batch of 100 μl in 20 mM Tris/HCl buffer pH 7.5 which comprises 5 mM MgCl_2 , 0.1 mg/ml bovine serum albumin and either 15 800 Bq $^3\text{HcAMP}$ or $^3\text{HcGMP}$. The end concentration of the corresponding nucleotide is 10^{-6} mol/l. The reaction is started by adding the enzyme, and the quantity of enzyme is such that approx. 50% of the substrate are converted during the incubation time of 30 minutes. To test the cGMP-stimulatable PDE II, $^3\text{HcAMP}$ is used as substrate, 10^{-6} mol/l unlabelled cGMP are added to the batch. To test the Ca- 20 calmodulin-dependent PDE I, 1 μM CaCl_2 and 0.1 μM calmodulin are also added to the reaction batch. The reaction is stopped by adding 100 μl of acetonitrile which contains 1 mM cAMP and 1 mM AMP. 100 μl of the reaction batch are separated by HPLC and the cleavage products are quantified on-line using a flow scintillation counter. The substance concentration at which the reaction rate is reduced by 50% is 25 measured. Also used for testing were the "Phosphodiesterase $[^3\text{H}]$ cAMP-SPA enzyme assay" and the "Phosphodiesterase $[^3\text{H}]$ cGMP-SPA enzyme assay" by Amersham Life Science. The test was performed following the manufacturer's protocol. To determine the PDE2 activity, the $[^3\text{H}]$ cAMP SPA assay was used, 10^{-6} M cGMP being added to the reaction batch for activating the enzyme. To 30 measure PDE1, 10^{-7} M calmodulin and 1 μM CaCl_2 were added to the reaction batch. PDE5 was measured using the $[^3\text{H}]$ cGMP SPA assay.

Phosphodiesterase inhibition in vitro

Example No.	PDE I IC ₅₀ [nM]	PDE II IC ₅₀ [nM]	PDE V IC ₅₀ [nM]
9	300	300	300
10	300	500	50
11	> 10,000	100	50
32	500	300	300
33	500	500	800

The compounds were tested for antihypertensive activity on the anaesthetized pig.

5 The erection-triggering effect was measured on the anaesthetized rabbit (C.G. Stief et al., World Journal Urology 1990, pp. 233-236).

The substances were applied directly into the corpus cavernosum, intraduodenally, rectally, orally, transdermally or intravenously at dosages from 0.03 to 10 mg/kg.

10 The new active compound can be converted in a known manner into the customary formulations such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert non-toxic pharmaceutically suitable excipients or solvents. The therapeutically active compound should be present in 15 each case in a concentration of approximately 0.5 to 90% by weight of the total mixture, i.e. in amounts which suffice to attain the dosage range indicated.

20 For example, the formulations are prepared by extending the active compounds with solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, it being possible, if appropriate, for organic solvents to be used as auxiliary solvents if, for example, water is used as the diluent.

Application is effected in the customary manner, preferably orally, transdermally or parenterally, in particular perlingually or intravenously.

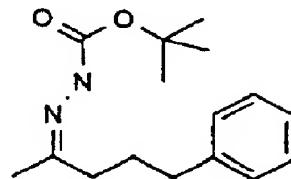
25 To achieve effective results, it has generally proved advantageous to administer, with intravenous application, amounts of approximately 0.01 to 10 mg/kg, preferably approximately 0.1 to 10 mg/kg bodyweight.

Nevertheless, it may be required to deviate from the abovementioned amounts, depending on the bodyweight or the route of application, the individual behaviour towards the medicament, the nature of its formulation and the point in time or interval at which it is administered. Thus, it may suffice in some cases to make do 5 with less than the abovementioned minimal amount, while the abovementioned upper limit will have to be exceeded in other cases. If larger amounts are administered, it may be recommendable to distribute them over the day in the form of several individual doses.

Starting compounds:

Example I

5 tert-Butyl N'-(1-methyl-4-phenyl-butylidene)-hydrazine-carboxylate



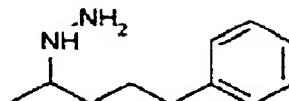
10.2 g (63 mmol) of 5-phenylpentan-2-one and 8.44 g (62 mmol) of tert-
10 butylcarbazate are dissolved in 100 ml of heptane, and stirred for 20 minutes at room temperature and for 60 minutes under reflux. The mixture is crystallized for 5 hours at 4°C, and the crystals are filtered off with suction, washed with pentane and dried.
Yield: 14.6g (96%).

R_f=0.15 (PE/EA=9:1)

15

Example II

(1-Methyl-4-phenyl-butyyl)-hydrazine



20

10.53 g (38 mmol) of tert-butyl N'-(1-methyl-4-phenyl-butylidene)-hydrazine-carboxylate are dissolved in 30 ml of THF and 40 ml of methanol, 2.77 g (44 mmol) of NaBH₃CN are added, and the mixture is stirred for 60 minutes at room temperature. After 27.2 ml of 6N HCl have been added dropwise, the mixture is refluxed for 60 minutes. It is neutralized with 6N sodium hydroxide solution, the non-aqueous solvents are distilled off, and the aqueous phase is extracted three times with ethyl acetate. The organic phase is dried over Na₂SO₄ and the solvent is removed in vacuo.

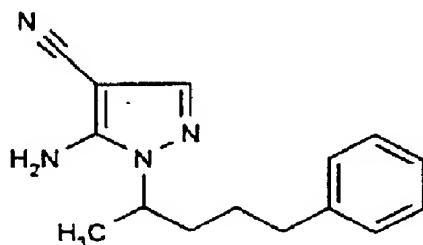
30

Yield: 6.78 g (99%) of a yellow oil.

$R_f=0.10$ (PE/EA=5:1)

Example III

5 5-Amino-1-(1-methyl-4-phenyl-butyl)-1*H*-pyrazol-4-carbonitrile



7.70 g (43 mmol) of (1-methyl-4-phenyl-butyl)-hydrazine 10 ml of methanol are
10 added to 5.28 g (43 mmol) of ethoxymethylenemalononitrile in 50 ml of methanol,
and the mixture is stirred for 15 minutes at room temperature. The mixture is
refluxed for 2 hours and the solvent is then removed in vacuo. The residue is taken
up in 100 ml of CH_2Cl_2 , the organic phase is extracted with saturated aqueous
15 NaHCO_3 solution, dried over Na_2SO_4 and a spatula-tip full of active charcoal, and
the solvent is removed in vacuo.

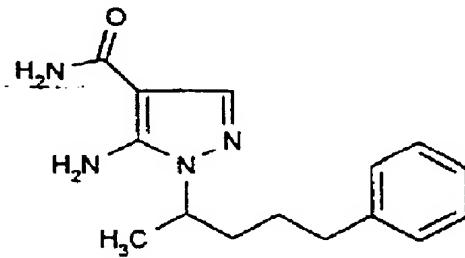
Yield: 9.70 g (88%) of a red oil.

$R_f=0.15$ (PE/EA=2:1)

Example IV

20

5-Amino-1-(1-methyl-4-phenyl-butyl)-1*H*-pyrazole-4-carboxamide



25 512 mg (2.02 mmol) of 5-amino-1-(1-methyl-4-phenyl-butyl)-1*H*-pyrazole-4-carbonitrile are stirred for 3 hours at room temperature with 25 ml of concentrated aqueous NH_3 , 20 ml of ethanol and 5 ml of 30% strength H_2O_2 . The non-aqueous

solvent is removed in vacuo, and the solid which has precipitated is filtered off with suction and dried.

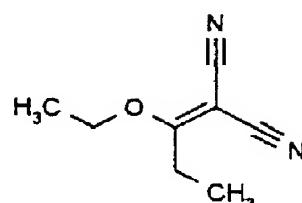
Yield: 408 mg (75%) of a white solid.

M.p.: 128°C

5

Example V

2-(1-Ethoxy-propylidene)-malononitrile



10

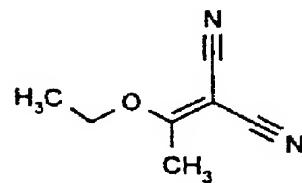
16.41 g (249 mmol) of malononitrile and 43.8 g (249 mmol) of triethyl orthopropionate are refluxed for 4.5 hours. The reaction mixture is cooled to room temperature and distilled in vacuo.

15 B.p.: 90°C (3 mbar)

Yield: 28.4g (75%)

Example VI

20 2-(1-Ethoxy-ethylidene)-malononitrile

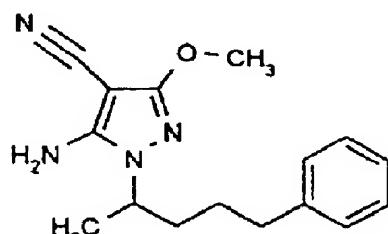


25 8.26 g (125 mmol) of malononitrile and 20.25 g (125 mmol) of triethyl orthoacetate are refluxed for 5 hours. After cooling, the mixture is dried in vacuo.

Yield: 16.0g (quantitative)

Example VII

5-Amino-3-ethyl-1-(1-methyl-4-phenyl-butyl)-1-*H*-pyrazole-4-carbonitrile



5

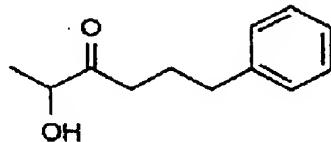
5 g (28 mmol) of (1-methyl-4-phenyl-butyl)-hydrazine and 4.17 g (28 mmol) of 2-(1-ethoxypropylidene)-malononitrile are refluxed for 2.25 hours in 150 ml of methanol. The solvent is removed in vacuo, the residue is taken up in 100 ml of CH_2Cl_2 , the 10 mixture is extracted with 0.1N HCl and saturated aqueous NaHCO_3 solution and dried over Na_2SO_4 , and the solvent is removed in vacuo.

Yield: 7.2 g (99%) of a red oil.

$R_f = 0.15$ (PE/EA=2:1).

15 **Example VIII**

2-Hydroxy-6-phenyl-hexane-3-one



20

7.3 (55 mmol) of trimethylsilyl cyanide are cooled to 0°C under argon, and 2 drops of BF_3OEt_2 and 3.1 ml (55 mmol) of acetaldehyde are added successively. The mixture is stirred for 1.5 h at room temperature, and the resultant cyanohydrin is dissolved in 10 ml of ether. 1 ml (6.6 mmol) of 3-phenyl-1-propyl bromide is added 25 to 1.3 g (55 mmol) of magnesium in 4 ml of ether under argon. After the spontaneous reaction has subsided, a further 7.4 ml (48.7 mmol) of 3-phenyl-1-propyl bromide, dissolved in 10 ml of ether are added dropwise at such a rate that gentle reflux is maintained. After the addition has ended, the mixture is refluxed for 30 minutes and then cooled to 0°C. The cyanohydrin solution is added dropwise at 0°C and the

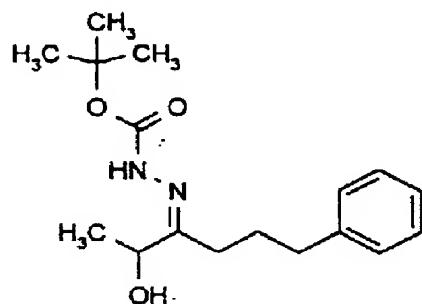
reaction mixture is stirred for 15 hours at room temperature. The reaction mixture is diluted with 100 ml of ether, poured into a mixture of 300 g of ice and 15 ml of concentrated H_2SO_4 and stirred for 3 hours at room temperature.. The ether phase is extracted three times with 10% strength HCl and once with saturated sodium chloride solution and dried over Na_2SO_4 , and the solvent is removed in vacuo.

5 Yield: 7.15 g (68%) of colourless oil

10 R_f : 0.12 (PE/EA=9:1)

Example IX

tert-Butyl N'-(1-methyl-4-phenyl-butylidene)-hydrazine-carboxylate



15 8.1 g (42 mmol) of 2-hydroxy-6-phenylhexan-3-one and 5.68 g of tert-butyl carbazate (43 mmol) are dissolved in 70 ml of heptane and 35 ml of THF and stirred for 30 minutes at room temperature and for 1.5 hours under reflux conditions. The solvent is removed in vacuo.

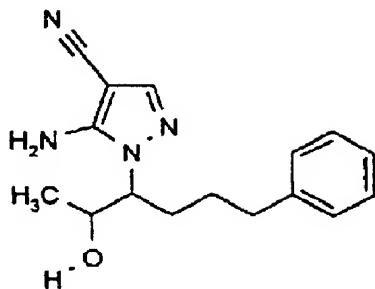
20 Yield: 12.81 g (99%) of yellow oil.

25 R_f : 0.10 (PE/EA=9:1).

Example X

5-Amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazole-4-carbonitrile

25

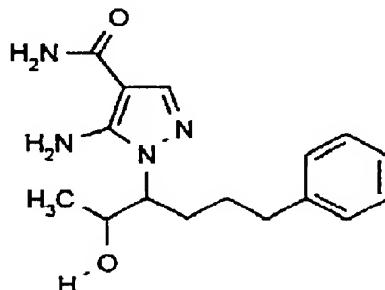


12.79 g (42 mmol) of tert-butyl N'-(1-methyl-4-phenyl-butylidene)hydrazinecarboxylate are dissolved in 30 ml of THF and 40 ml of methanol, 6.08 g (97 mmol) of NaBH₃CN are added, and the mixture is stirred for 60 minutes at room temperature. After 35 ml of 6N HCl have been added dropwise, the mixture is refluxed for 60 minutes. It is neutralized with 6N sodium hydroxide solution and extracted three times with CH₂Cl₂. The organic phase is dried over Na₂SO₄ and the solvent is removed in vacuo. This gives 7.38 g of a pale yellow oil. 6.5 g of this oil are first stirred with 3.93 g (32 mmol) of ethoxymethylenemalononitrile in 200 ml of methanol for one hour at room temperature and then refluxed for 2 hours. After cooling, the solvent is removed in vacuo. Purification by chromatography (PE/EA=2:1) gives 5.28g of a colourless oil.
 R_f: 0.10 (PE/EA=2:1).

15

Example XI

5-Amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1H-pyrazole-4-carboxamide



20

3.9 g (13.7 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1H-pyrazole-4-carbonitrile and 960 mg of tetrabutylammonium hydrogen sulphate are dissolved in 28 ml of CH₂Cl₂, 5.5 ml of 5M NaOH and 7 ml of 30% strength H₂O₂ are added, and the mixture is stirred for 4 hours at room temperature. The phases are separated, the

organic phase is extracted twice with water, the organic phase is dried over Na_2SO_4 , and the solvent is removed in vacuo.

Yield: 3.8g (92%)

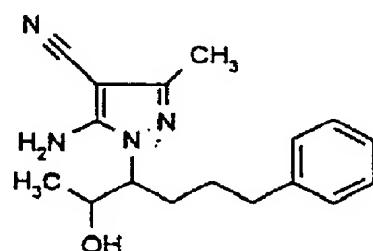
M.p.:116°C (PE/EA)

5

Example XII

5-Amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1*H*-pyrazole-4-carbonitrile

10



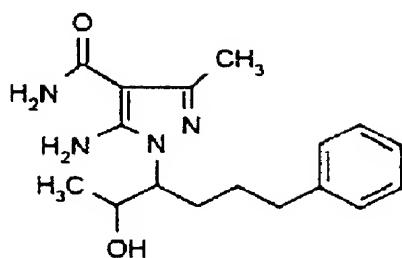
12.79 g (42 mmol) of tert-butyl N'-(1-methyl-4-phenyl-butylidene)-hydrazinecarboxylate are dissolved in 30 ml of THF and 40 ml of methanol, 6.08 g (97 mmol) of NaBH_3CN are added, and the mixture is stirred for 60 minutes at room temperature. After 35 ml of 6N HCl have been added dropwise, the mixture is refluxed for 60 minutes. It is neutralized with 6N sodium hydroxide solution and extracted three times with CH_2Cl_2 . The organic phase is dried over Na_2SO_4 and the solvent is removed in vacuo. This gives 7.38 g of a pale yellow oil. 2.64 g of this oil (11.3mmol) and 1.4g of 2-(1-ethoxy-ethylidene)-malononitrile (11.3mmol) are refluxed for 2 hours in 20 ml of methanol. The solvent is removed in vacuo. 3.73g of a red oil.

R_f 0.11 (PE/EA=2:1)

25

Example XIII

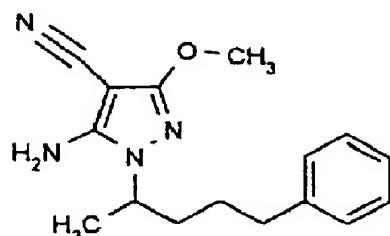
5-Amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1*H*-pyrazole-4-carboxamide



3.7 g (12.37 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3methyl-1H-pyrazole-4-carbonitrile and 950 mg of tetrabutylammonium hydrogen sulphate are dissolved in 25 ml of CH_2Cl_2 , 5.5 ml of 5M NaOH and 7 ml of 30% strength H_2O_2 are added, and the mixture is stirred for 15 hours at room temperature. The phases are separated, the organic phase is extracted twice with water, the organic phase is dried over Na_2SO_4 , and the solvent is removed in vacuo. Yield: 3.24g (83%), $R_f=0.11$ (petroleum ether/ethyl acetate = 1:1)

10 Example XIV

5-Amino-4-cyano-3-methoxy-1-[(5-phenyl)-pent-2-yl]-pyrazole

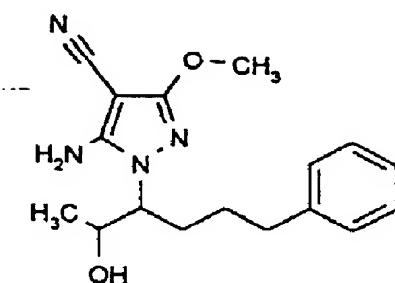


15 3.6 g of 2-hydrazino-5-phenylpentane are dissolved in 40 ml of methanol, and 2.8 ml of triethylamine are added. Then, 2.8 g of 1,1-dimethoxy-2,2-dicyanoethylene are added at approx. 0°C. The reaction solution is warmed to approx. 20°C and stirred for 1.5 hours at approx. 20°C. For work-up, the mixture is diluted with water, acidified with citric acid and extracted twice with dichloromethane. The combined dichloromethane phases are dried with magnesium sulphate and evaporated in vacuo. This gives 5.1 g of a yellow oil, which crystallizes slowly. The oil is chromatographed on silica gel (Merck Si 60 0.04-0.063 mm) with a petroleum ether/ethyl acetate mixture in a ratio of 5:1 to 1:1. This gives a fraction which, after evaporation in vacuo, affords 4.6 g (=80.9% of theory) of 5-amino-4-cyano-3-methoxy-1-[(5-phenyl)-pent-2-yl]-pyrazole.

NMR(400MHZ, CD3OD): 1.3[3]d J=8Hz; 1.4-1.65[3]m; 1.85-1.95[1]m; 2.5-2.65[2]m; 3.85[3]s; 4.1-4.2[1]m; 7.1-7.15[3]m; 7.2-7.25[2]m
TLC RF value=0.6; eluent: petroleum ether/ethyl acetate 1:1; Merck Si60

5 Example XV

5-Amino-4-cyano-3-methoxy-1-[2-hydroxy-6-phenyl-hex-3-yl]-pyrazole



10

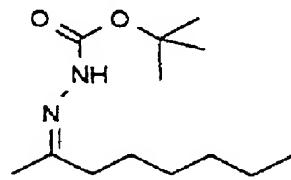
4.2 g of 3-hydrazino-2-hydroxy-6-phenylhexane are dissolved in 20 ml of methanol, and 1.38 ml of triethylamine are added. Then, 1.38 g of 1,1-dimethoxy-2,2-dicyano-ethylene are added. The reaction solution is stirred for 2 hours at approx. 20°C. For work-up, the mixture is diluted with citric acid solution and ethyl acetate and extracted three times with ethyl acetate. The combined ethyl acetate phases are dried with magnesium sulphate and evaporated in vacuo. The evaporation residue is chromatographed on silica gel (Merck Si 60 0.04-0.063 mm) with a cyclohexane/ethyl acetate mixture in a ratio of 4:1 to 1:1. This gives a fraction which, after evaporation in vacuo, affords 0.959 g (=30.5% of theory) of 5-amino-4-cyano-3-methoxy-1-[2-hydroxy-6-phenyl-hex-3-yl]-pyrazole as diastereomer mixture.

15 TLC RF value = 0.2; eluent: dichloromethane/methanol 10:1; Merck Si60 Art.No. 1.05719

Example XVI

25

tert-Butyl N'-(1-methyl-heptylidene)-hydrazinecarboxylate



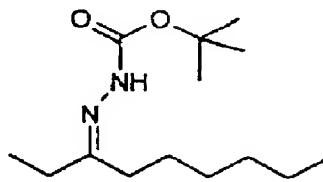
40 g (312 mmol) of 2-octanone and 41.23 g (312 mmol) of tert-butyl carbazate are refluxed for 2 hours in 350 ml of cyclohexane. The solvent and water are removed in vacuo. This gives 74.10 g (98%) of a waxy solid.

5 200 MHz ^1H NMR (2 isomers) (ppm, CDCl_3): 7.49, s, broad, 1H; 7.38, s, broad, 1H; 2.29, m, 2H; 2.12, m, 2H; 2.00, s, 3H; 1.79, s, 3H; 1.51, m, 11H; 1.29, m, 6H; 0.88, m, 3H.

Example XVII

10

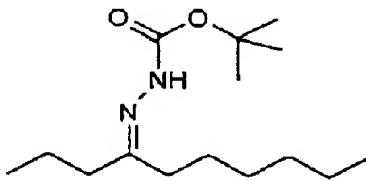
tert-Butyl N'-(1-ethyl-heptylidene)-hydrazinecarboxylate



15 16.42 g (115 mmol) of 3-nonenone and 15.26 g (115.4 mmol) of tert-butyl carbazate are refluxed for 3 hours in 200 ml of cyclohexane. The solvent is removed in vacuo. This gives 30.54 g (product contains water) of a white solid, $R_f = 0.49$ (cyclohexane/ethyl acetate = 3:1).

20 **Example XVIII**

tert-Butyl N'-(1-propyl-heptylidene)-hydrazinecarboxylate



25

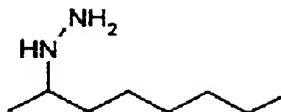
24.76 g (158 mmol) of 4-decanone and 20.94 g (158 mmol) of tert-butyl carbazate are heated for 90 minutes at 80°C in 250 ml of cyclohexane/heptane mixture (1:1). After cooling, 39.71 g (93%) of a white solid are obtained by crystallization.

200 MHz ^1H NMR (ppm, CDCl_3): 7.49, s, broad, 1H; 2.20, m, 4H; 1.51, m, 13H; 1.30, m, 6H; 0.91, m, 6H.

Example XIX

(1-Methyl-heptyl)-hydrazine

5



74.08 g (305.7 mmol) of tert-butyl N'-(1-methyl-heptylidene)-hydrazinecarboxylate are dissolved in a mixture of 235 ml of THF and 310 ml of methanol and, after 22.34 g (354.6 mmol) of sodium cyanoborohydride have been added, the mixture is 10 stirred for 1 hour at room temperature. 213 ml of 6N HCl are added dropwise and, after the addition has ended, the mixture is refluxed for 1.5 hours. It is neutralized with 6N NaOH solution, then, after the non-aqueous solvents have been removed, extracted three times with dichloromethane, and, after the mixture has been dried over sodium sulphate, the solvent is removed in vacuo. This gives 37.5 g (85%) of a 15 yellow oil.

400 MHz ¹H NMR (ppm, CDCl₃): 3.18, s, broad, 3H, 2.52, m, 1H; 1.28, m, 9H; 1.07, d, 3H; 0.89, m, 4H.

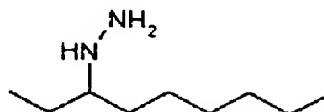
Example XX

20

(1-Ethyl-heptyl)-hydrazine

25

34.84 g (135.9 mmol) of tert-butyl N'-(1-ethyl-heptylidene)-hydrazinecarboxylate are dissolved in a mixture of 100 ml of THF and 150 ml of methanol and, after 9.93 g (157.6 mmol) of sodium cyanoborohydride have been added, the mixture is stirred for 2 hours at room temperature. 97 ml of 6N HCl are added dropwise and, after the addition has ended, the mixture is refluxed for 1.5 hours. It is neutralized with 6N NaOH solution, then, after the non-aqueous solvents have been removed, extracted three times with dichloromethane, and, after the mixture has been dried 30



over sodium sulphate, the solvent is removed in vacuo. This gives 19.78 g (92%) of a yellow oil.

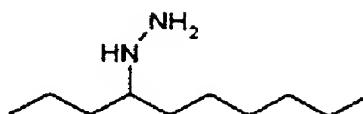
200 MHz ^1H NMR (ppm, CDCl_3); 3.68, s, broad, 3H, 2.48, m, 1H; 1.32, m, 12H; 0.90, m, 6H.

5

Example XXI

(1-Propyl-heptyl)-hydrazine

10



15

20

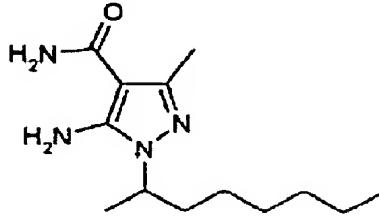
39.41 g (145.7 mmol) of tert-butyl N'-(1-propyl-heptylidene)-hydrazinecarboxylate are dissolved in a mixture of 100 ml of THF and 150 ml of methanol and, after 10.65 g (169 mmol) of sodium cyanoborohydride have been added, the mixture is

stirred for 1 hour at room temperature. 100 ml of 6N HCl are added dropwise in the course of 30 minutes and, after the addition has ended, the mixture is refluxed for 1 hour. The mixture is neutralized with 6N NaOH solution, then, after the non-aqueous solvents have been removed, extracted three times with dichloromethane, and, after the mixture has been dried over sodium sulphate, the solvent is removed in vacuo. This gives 23.90 g (95%) of a yellow oil.

200 MHz ^1H NMR (ppm, CDCl_3); 3.20, s, broad, 3H; 2.50, m, 1H; 1.20, m, 13H; 0.90, m, 6H.

25

5-Amino-3-methyl-1-(2-octyl)-1-*H*-pyrazole-4-carboxamide



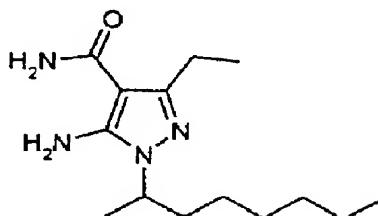
4.72 g (34.66 mmol) of 2-(1-ethoxy-ethylidene)-malononitrile and 5.00 g (34.66 mmol) of (1-methyl-heptyl)-hydrazine are refluxed for 4 hours in 40 ml of methanol. After the solvent has been removed in vacuo, 8.23 g of a red oil are obtained. This is dissolved in 250 ml of ethanol and, after 300 ml of concentrated 5 NH₃ solution (25% strength) and 70 ml of hydrogen peroxide solution (30% strength) have been added, the solution is stirred for 65 hours at room temperature. After the non-aqueous solvents have been removed, the mixture is extracted three times with dichloromethane, and the organic phase is dried over sodium sulphate and evaporated on a rotary evaporator. This gives 7.75 g (87%) of a red oil.

10

Example XXIII

5-Amino-3-ethyl-1-(2-octyl)-1-*H*-pyrazole-4-carboxamide

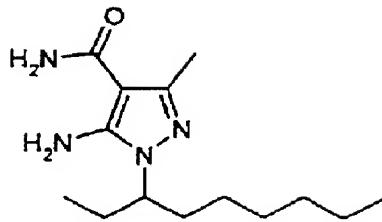
15



5.21 g (34.66 mmol) of 2-(1-ethoxy-propylidene)-malononitrile and 5.00 g (34.66 mmol) of (1-methyl-heptyl)-hydrazine are refluxed for 4 hours in 40 ml of methanol. After the solvent has been removed in vacuo, 8.60 g of a red oil are obtained. The latter is dissolved in 250 ml of ethanol and, after 300 ml of concentrated NH₃ solution (25% strength) and 70 ml of hydrogen peroxide solution (30%) have been added, the mixture is stirred for 48 hours at room temperature. After the non-aqueous solvents have been removed, the mixture is extracted three times with dichloromethane, and the organic phase is dried over sodium sulphate and evaporated on a rotary evaporator. This gives 7.45 g (71%) of a red solid.

Example XXIV

30 5-Amino-3-methyl-1-(3-nonyl)-1-*H*-pyrazole-4-carboxamide



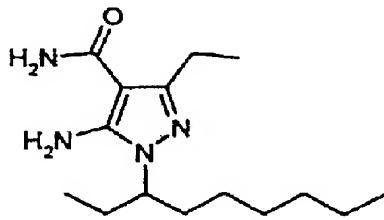
3.13 g (19.79 mmol) of (1-ethyl-heptyl)-hydrazine and 2.69 g (19.79 mmol) of 2-(1-ethoxy-ethylidene)-malononitrile are refluxed for 4 hours in 30 ml of methanol.

5 After the solvent has been removed, 4.84 g of a red oil are obtained. The latter is dissolved in 150 ml of ethanol and, after 180 ml of concentrated NH₃ solution (35% strength) of 40 ml of hydrogen peroxide solution (30% strength) have been added, the mixture is stirred for 48 hours at room temperature. After the non-aqueous solvents have been removed, the mixture is extracted three times with dichloromethane, and the organic phase is dried over sodium sulphate and evaporated on a rotary evaporator. This gives 4.13 g (78%) of a red oil.

10

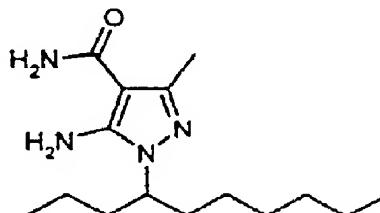
Example XXV

15 5-Amino-3-ethyl-1-(3-nonyl)-1H-pyrazole-4-carboxamide



20 3.16 g (19.96 mmol) of (1-ethyl-heptyl)-hydrazine and 3.00 g (19.96 mmol) of 2-(1-ethoxy-propylidene)-malononitrile are refluxed for 4 hours in 30 ml of methanol. After the solvent has been removed, 5.102 g of a red oil are obtained. 4.70 g of this oil are dissolved in 150 ml of ethanol and, after 180 ml of concentrated NH₃ solution (25% strength) and 40 ml of hydrogen peroxide solution (30% strength) have been added, the solution is stirred for 65 hours at room temperature. After the non-aqueous solvents have been removed, the mixture is extracted three times with dichloromethane, and the organic phase is dried over sodium sulphate and evaporated on a rotary evaporator. This gives 4.83 g (96%) of a red oil.

25

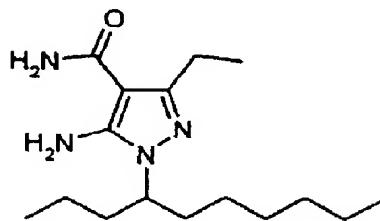
Example XXVI5-Amino-3-methyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide

5

3.79 g (22 mmol) of (1-propyl-heptyl)-hydrazine and 2.99 g (22 mmol) of 2-(1-ethoxy-ethylidene)-malononitrile are refluxed for 4 hours in 30 ml of methanol. After the solvent has been removed, 5.86 g of a red oil are obtained. 5.19 g of this oil are dissolved in 150 ml of ethanol and, after 180 ml of concentrated NH₃ solution (25% strength) of 40 ml of hydrogen peroxide solution (30% strength) have been added, the mixture is stirred for 65 hours at room temperature. After the non-aqueous solvents have been removed, the mixture is extracted three times with dichloromethane, and the organic phase is dried over sodium sulphate and evaporated on a rotary evaporator. This gives 4.35 g (79%) of a yellow oil.

Example XXVII5-Amino-3-ethyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide

20

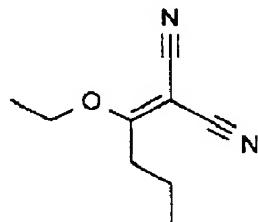


3.44 g (19.96 mmol) of (1-propyl-heptyl)-hydrazine and 3.0 g (19.96 mmol) of 2-(1-ethoxy-propylidene)-malononitrile are refluxed for 4 hours in 30 ml of methanol. After the solvent has been removed, 5.75 g of a red oil are obtained. 5.12 g of this oil are dissolved in 150 ml of ethanol and, after 180 ml of concentrated NH₃ solution (25% strength) and 40 ml of hydrogen peroxide solution (30% strength) have been added, the solution is stirred for 65 hours at room temperature. After the

non-aqueous solvents have been removed, the mixture is extracted three times with dichloromethane, and the organic phase is dried over sodium sulphate and evaporated on a rotary evaporator. This gives 5.11 g (86%) of a yellow wax.

5 Example XXVIII

2-(1-ethoxy-butylidene)-malononitrile



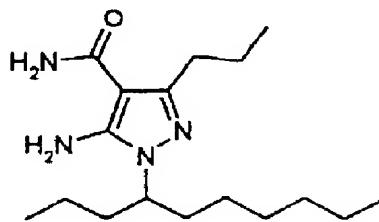
10

18.69 g (283 mmol) of malononitrile and 41.94 g (283 mmol) of triethylorthobutyrate are heated for 4 hours at 150°C. The reaction mixture is cooled to room temperature and, after the ethanol has been removed, distilled in vacuo. B.p.: 85°C (3mbar). Yield: 32.05 g (76%).

15

Example XXIX

5-Amino-3-propyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide



20

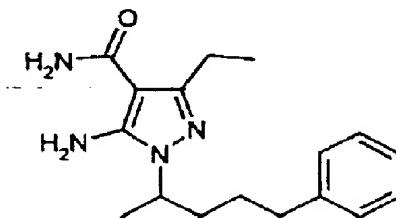
3.15 g (18.28 mmol) of (1-propyl-heptyl)-hydrazine and 3.0 g (18.28 mmol) of 2-(1-ethoxybutylidene)-malononitrile are refluxed for 4 hours in 30 ml of methanol. After the solvent has been removed, 5.57 g of a red oil are obtained. 4.99 g of this oil are dissolved in 150 ml of ethanol and, after 180 ml of concentrated NH3 solution (25% strength) and 40 ml of hydrogen peroxide solution (30% strength) have been added, the solution is stirred for 65 hours at room temperature. After the non-aqueous solvents have been removed, the mixture is extracted three times with

dichloromethane, and the organic phase is dried over sodium sulphate and evaporated on a rotary evaporator. The residue is dissolved in 150 ml of ethanol and, after 180 ml of concentrated NH₃ solution and 40 ml of hydrogen peroxide solution have been added, the solution is stirred for 65 hours at room temperature. After the non-aqueous solvents have been removed, the mixture is extracted three times with dichloromethane, and the organic phase is dried over sodium sulphate and evaporated on a rotary evaporator. This gives 4.89 g (92%) of a yellow oil.

Example XXX

10

5-Amino-3-ethyl-1-(1-methyl-4-phenyl-butyl)-1-*H*-pyrazole-4-carboxamide

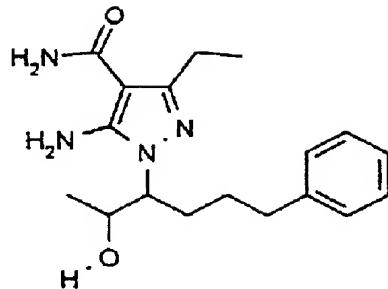


15 5.08 g (18 mmol) of 5-amino-3-ethyl-1-(1-methyl-4-phenyl-butyl)-1-*H*-pyrazole-4-carbonitrile are dissolved in 100 ml of ethanol and, after 100 ml of concentrated NH₃ solution (25% strength) and 50 ml of hydrogen peroxide solution (30% strength) have been added, the solution is stirred for 16 hours at room temperature. After the non-aqueous solvents have been removed, the pH is brought to 5 with 1N HCl. The 20 aqueous phase is extracted three times with dichloromethane, and the organic phase is dried over sodium sulphate and evaporated on a rotary evaporator. This gives 3.58 g of a brown oil (66%).

Example XXXI

25

5-Amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-ethyl-1*H*-pyrazole-4-carboxamide

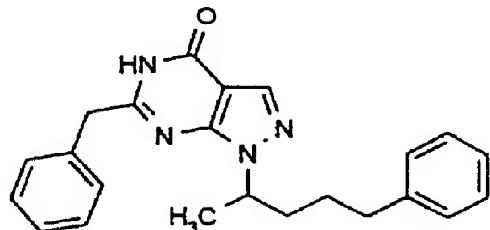


12.79 g (42 mmol) of tert-butyl N'-(1-methyl-4-phenyl-butylidene)-5
hydrazinecarboxylate are dissolved in 30 ml of THF and 40 ml of methanol, 6.08 g
10 (97 mmol) of NaBH₃CN are added, and the mixture is stirred for 60 minutes at room
temperature. After 35 ml of 6N HCl have been added dropwise, the mixture is
refluxed for 60 minutes. It is neutralized with 6N sodium hydroxide solution and
extracted three times with CH₂Cl₂. The organic phase is dried over Na₂SO₄ and the
solvent is removed in vacuo. This gives 7.38 g of a pale yellow oil. 3.00 g of this oil
15 (14.4 mmol) and 2.50 g of 2-(1-ethoxy-propylidene)-malononitrile (16.6 mmol) are
refluxed for 3 hours in 25 ml of methanol. The solvent is removed in vacuo. 4.238 g
of a red oil. R_f = 0.15. (PE/EA = 2:1). This oil is dissolved in 136 ml of ethanol and,
after 170 ml of concentrated NH₃ solution and 34 ml of 30% strength hydrogen
peroxide solution have been added, the solution is stirred for 18 hours at room
15 temperature. After the non-aqueous solvents have been removed in vacuo, the
mixture is extracted three times with dichloromethane, the organic phase is dried
over sodium sulphate, the solvent is removed in vacuo. This gives 2.55 g (53%
strength) of a red oil. R_f=0.15 (PE/EA = 1:1).

Preparation Examples

Example 1

5 6-Benzyl-1-(1-methyl-4-phenyl-butyl)-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-ones



870 mg (3.42 mmol) of 5-amino-1-(1-methyl-4-phenyl-butyl)-1H-pyrazol-
10 4-carbonitrile and 70 mg of DMAP are dissolved in 5 ml of pyridine, and a solution
of 582 mg (3.78 mmol) of phenylacetyl chloride in 2 ml of toluene is added
dropwise. The solution is stirred for 30 minutes at room temperature and for 2 hours
at 60°C, the solvent is removed in vacuo, the residue is taken up in 50 ml of CH₂Cl₂,
the organic phase is extracted with 1N HCl and saturated aqueous NaHCO₃ and dried
15 over Na₂SO₄, and the solvent is removed in vacuo.

The residue is refluxed for 15 hours in 30 ml of water and 16 ml of ethanol together
with 2 g of K₂CO₃ and 4 ml of 30% strength H₂O₂. After the reaction mixture has
been acidified with 1N HCl, it is extracted with ethyl acetate, the organic phase is
20 dried over Na₂SO₄ and the solvent is removed in vacuo. Purification by
chromatography (petroleum ether/ethyl acetate) gives 450 mg (35%) of a solid. M.p.:
136°C.

The compounds listed in Table 1 are obtained analogously to the protocol of
25 Example 1:

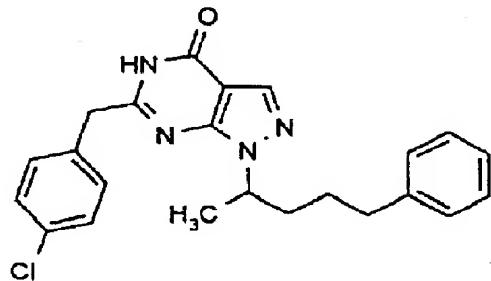
Table 1

Ex. No.	Structure	$\text{F}^\circ\text{C} / \text{R}_t$	Yield (% of Theory)
2		158	456 mg (42%)
3		163	398 mg (36%)
4		104	353 mg (32%)
5		167	164 mg (14%)
6		203	196 mg (2.5%)

Example 7

6-(4-Chloro-benzyl)-1-(1-methyl-4-phenyl-butyl)-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-ones

5



400 mg (1.47 mmol) of 5-amino-1-(1-methyl-4-phenyl-butyl)-1*H*-pyrazole-4-carboxamide and 80 mg of DMAP are dissolved in 12 ml of pyridine, and a
10 solution of 457 mg (2.43 mmol) of p-chlorophenylacetyl chloride in 1 ml of toluene is added dropwise. The solution is stirred for 3.5 hours at 60°C, the solvent is removed in vacuo, the residue is taken up in 50 ml of CH₂Cl₂, the organic phase is extracted with 1N HCl and saturated aqueous NaHCO₃ and dried over Na₂SO₄, and the solvent is removed in vacuo.

15

The residue is refluxed for 3 hours in 4 ml of water, 15 ml of methanol and 7 ml of ethanol together with 700 mg of NaOH. The non-aqueous solvents are removed in vacuo, the residue is acidified with 1N HCl and then extracted with ethyl acetate, the organic phase is dried over Na₂SO₄, and the solvent is removed in vacuo. Purification by chromatography (petroleum ether/ethyl acetate) gives 380 mg (64%) M.p.: 20 168°C.

The compounds listed in Table 2 are obtained analogously to the protocol of Example 7:

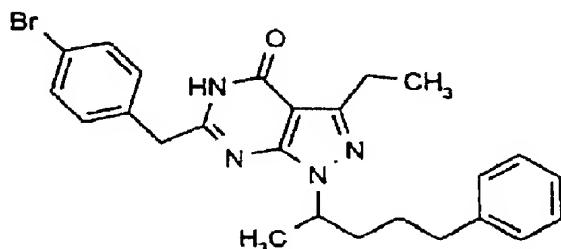
Table 2

Ex. No.	Structure	$\text{F}^\circ\text{C} / \text{R}_t$	Yield (% of Theory)
8		56	820 mg (85%)
9		125	782 mg (79%)
10		56	800 mg (76%)

5 Example 11

6-(4-Bromo-benzyl)-1-(1-methyl-4-phenyl-butyl)-3-ethyl-1,5-dihydro-pyrazole[3,4-d]pyrimidin-4-one

10



2.93 g (10.39 mmol) of 5-amino-3-ethyl-1-(1-methyl-4-phenyl-butyl)-1-H-pyrazole-4-carbonitrile and 250 mg of 4-dimethylaminopyridine are dissolved in 24 ml of pyridine, and a solution of 2.91 g (12.54 mmol) of 4-bromophenylacetyl chloride in 15 7 ml of toluene is added. The mixture is stirred for 2.5 hours at 60°C, the solvent is removed in vacuo, and the residue is taken up in 100 ml of CH_2Cl_2 . The mixture is extracted with 1N HCl, saturated NaHCO_3 solution and water, the extract is dried

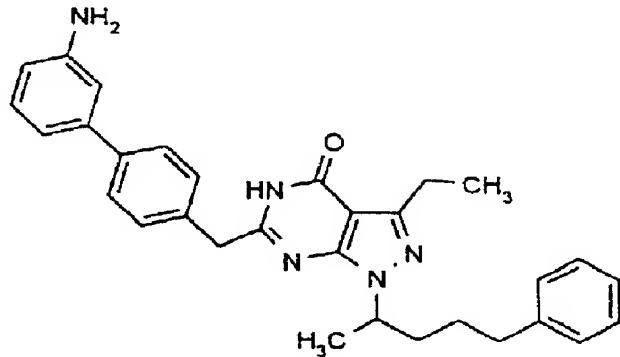
over Na_2SO_4 , and the solvent is removed in vacuo. The crude product is dissolved in 24 ml of pyridine, and a solution of 2 g (8.62 mmol) of 4-bromophenylacetyl chloride in 5 ml of toluene is added. The mixture is stirred for 2.5 hours at 60°C, the solvent is removed in vacuo, the residue is taken up in 100 ml of CH_2Cl_2 . The mixture is 5 extracted with 1N HCl, saturated NaHCO_3 solution and water, the extract is dried over Na_2SO_4 , and the solvent is removed in vacuo.

The reaction product is dissolved in 370 ml of ethanol and, after 600 ml of 1N NaOH and 70 ml of H_2O_2 (30% strength) have been added, the solution is stirred for 5 hours 10 at 90°C. The solvent is removed in vacuo, 1N HCl is added and the mixture then extracted three times with CH_2Cl_2 , the extract is dried over Na_2SO_4 and the solvent is removed in vacuo. Purification by chromatography (CH_2Cl_2 /methanol = 20:1) and crystallization from ether give 150 mg (3%) of a colourless solid.

15 M.p.: 112°C.

Example 12

20 6-(3'-Amino-biphenyl-4-yl-methyl)-3-ethyl-1-(1-methyl-4-phenyl-butyl)-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



25 697 mg (4.5 mmol) of 3-aminophenylboronic acid monohydrate and 150 mg of tetrakis(triphenylphosphine)-palladium are added under argon to a solution of 1.66 g (3.47 mmol) of 6-(4-bromo-benzyl)-1-(1-methyl-4-phenyl-butyl)-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one in 38 ml of THF, and the mixture is stirred for one hour at 70°C. After 4.9 ml of 1N Na_2CO_3 solution have been added, the mixture is stirred for a further 4 hours at 70°C, the solvent is removed in vacuo, and

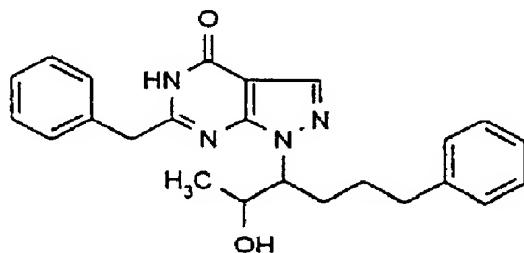
the residue is taken up in CH_2Cl_2 . The mixture is extracted with 2N HCl, and the aqueous phase is rendered alkaline with 1N NaOH and extracted twice with CH_2Cl_2 . After the extract has been dried over Na_2SO_4 , the solvent is removed in vacuo. Purification by chromatography (toluene/ethyl acetate = 4:1) gives 110 mg (6.4%) of

5 a pale yellow solid.

M.p.: 108°C

Example 13

10 6-Benzyl-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1,5-dihydro-pyrazolo[3,4-
d]pyrimidin-4-one



15 230 mg (0.76 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazole-4-carboxamide and 50 mg of 4-dimethylaminopyridine are dissolved in 5 ml of pyridine, and a solution of 293 mg (1.9 mmol) of phenylacetal chloride in 0.5 ml of toluene is added. The mixture is stirred for 3 hours at 50°C, the solvent is removed in vacuo, and the residue is taken up in 100 ml of CH_2Cl_2 . The mixture is extracted with 1N HCl, saturated in NaHCO_3 solution and water, the extract is dried over Na_2SO_4 , the solvent is removed in vacuo.

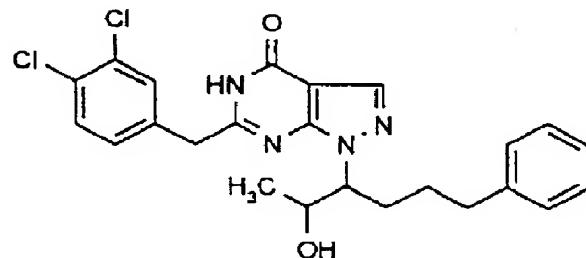
20

The reaction product is dissolved in 8 ml of methanol and 2 ml of ethanol, 2 ml of water and 350 mg of NaOH are added, and the mixture is refluxed for 3 hours. The 25 solvents are removed in vacuo, 1 N HCl is added and the mixture is then extracted twice with EtOAc, the extract is dried over Na_2SO_4 and the solvent is removed in vacuo. Purification by chromatography (PE/EA = 2:1) gives 101 mg (33%) of a diastereomer mixture, $R_f = 0.09$ (PE/EA = 1:1) and 10 mg (3.3%) of the pure diastereomer, which elutes later.

Example 14 and Example 15

6-(3,4-Dichloro-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1,5-dihydro-pyrazolo-[3,4-*d*]pyrimidin-4-one

5

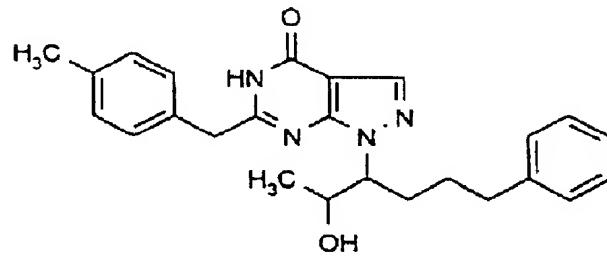


Starting from 400 g (1.32 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazole-4-carboxamide and 735 mg (3.31 mmol) of 3,4-dichlorophenylacetal chloride, the title compound is prepared analogously to the protocol of Example 13. This gives 65 mg (10.4%) of the diastereomer which elutes more rapidly, M.p.: 172°C, and 63 mg (10%) of the diastereomer which elutes more slowly, M.p.: 161°C.

Example 16 and Example 17

15

1-[1-(1-Hydroxy-ethyl)-4-phenyl-butyl]-6-(4-methyl-benzyl)-1,5-dihydro-pyrazolo[3,4-*d*]-pyrimidin-4-one

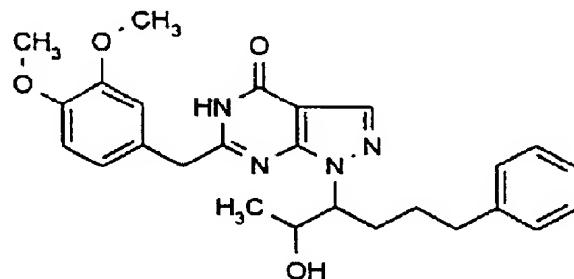


20

Starting from 400 g (1.32 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazole-4-carboxamide and 578 mg (3.44 mmol) of 4-methylphenylacetylchloride, the title compound is prepared analogously to the protocol of Example 13. This gives 117 mg (21%) of the diastereomer which elutes more rapidly, M.p.: 133°C, and 75 mg (13.6%) of the diastereomer which elutes more slowly, M.p.: 136°C.

Example 18

5 6-(3,4-Dimethoxy-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1,5-dihydro-pyrazolo-[3,4-*d*]pyrimidin-4-one



10 Starting from 400 mg (1.32 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazol-4-carboxamide and 711 mg (3.32 mmol) of 3,4-dimethoxyphenylacetylchloride, the title compound is obtained analogously to the protocol of Example 13.

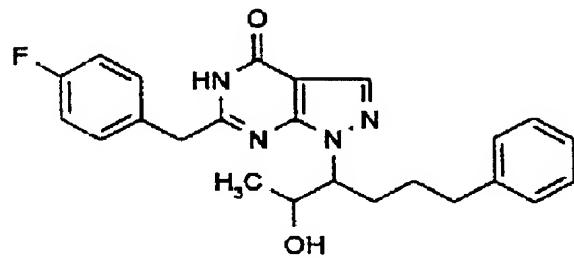
Yield: 303 mg (50%).

M.p.: 85°C.

15

Example 19 and Example 20

20 6-(4-Fluoro-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1,5-dihydro-pyrazolo-[3,4-*d*]pyrimidin-4-one



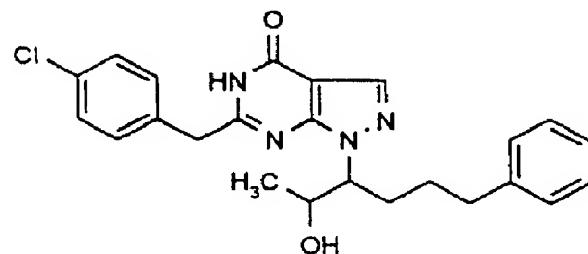
25 Starting from 400 mg (1.32 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazole-4-carboxamide and 570 mg (3.31 mmol) of 4-fluorophenylacetyl chloride, the title compounds are prepared analogously to the protocol of Example 13. This gives 143 mg (27%) of the diastereomer which elutes more rapidly, M.p.

103°C, and 111 mg (21%) of the diastereomer which elutes more slowly, M.p.: 107°C.

Example 21 and Example 22

5

6-(4-chloro-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1,5-dihydro-pyrazolo-[3,4-*d*]pyrimidin-4-one



10

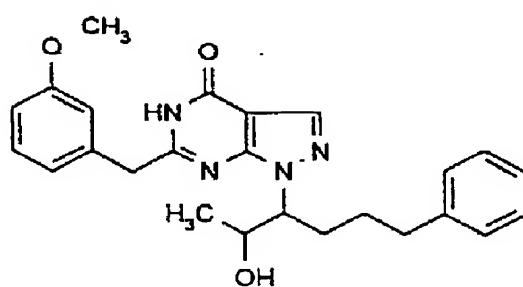
Starting from 400 mg (1.32 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazole-4-carboxamide and 626 mg (3.77 mmol) of 4-chlorophenylacetyl chloride, the title compounds are prepared analogously to the protocol of Example 13. This gives 150 mg (26%) of the diastereomer which elutes more rapidly, M.p.: 125°C, and 90 mg (16%) of the diastereomer which elutes more slowly, M.p.: 101°C.

15

Example 23 and Example 24

20

1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-6-(3-methoxy-benzyl)-1,5-dihydro-pyrazolo-[3,4-*d*]pyrimidin-4-one



25

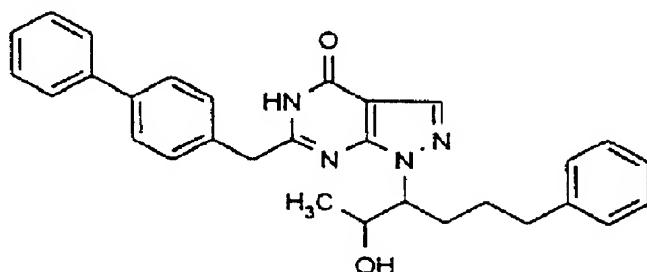
Starting from 400 mg (1.32 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazole-4-carboxamide and 610 mg (3.81 mmol) of 3-methoxyphenylacetyl chloride, the title compounds are prepared analogously to the

protocol of Example 13. This gives 160 mg (28%) of the diastereomer which elutes more rapidly, M.p.: 92°C, and 145 mg (25%) of the diastereomer which elutes more slowly, M.p.: 54°C.

5 **Example 25 and Example 26**

6-biphenyl-4-yl-methyl-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1,5-dihydro-pyrazolo-[3,4-*d*]pyrimidin-4-one

10

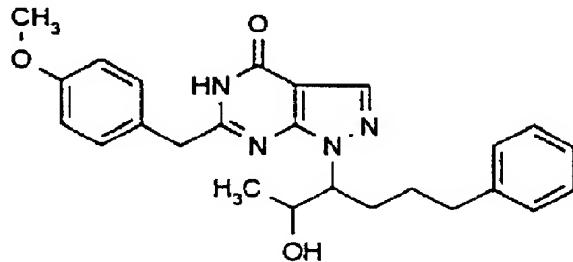


Starting from 954 mg (3.16 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazole-4-carboxamide and 1.82 g (7.91 mmol) of 4-phenylphenylacetyl chloride, the title compounds are prepared analogously to the protocol of Example

15 13. This gives 410 mg (27%) of the diastereomer which elutes more rapidly, M.p.: 90°C, and 160 mg (11%) of the diastereomer which elutes more slowly, M.p.: 142°C.

Example 27 and Example 28

20 1-[1-(1-Hydroxy-ethyl)-4-phenyl-butyl]-6-(4-methoxy-benzyl)-1,5-dihydro-pyrazolo-[3,4-*d*]pyrimidin-4-one



25 Starting from 1 g (3.31 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazole-4-carboxamide and 1.52 g (8.26 mmol) of 4-methoxyphenylacetyl

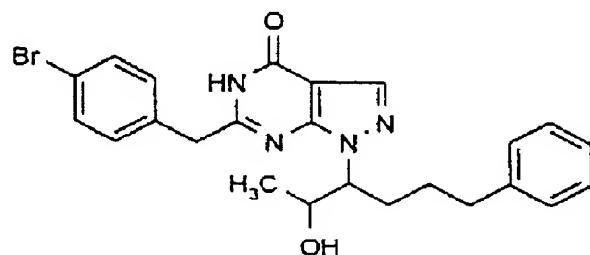
chloride, the title compounds are prepared analogously to the protocol of Example 13. This gives 240 mg (17%) of the diastereomer which elutes more rapidly, M.p.: 41°C, and 134 mg (9%) of the diastereomer which elutes more slowly, M.p.: 48°C.

5

Example 29 and Example 30

6-(4-bromo-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1,5-dihydro-pyrazolo-[3,4-*d*]pyrimidin-4-one

10



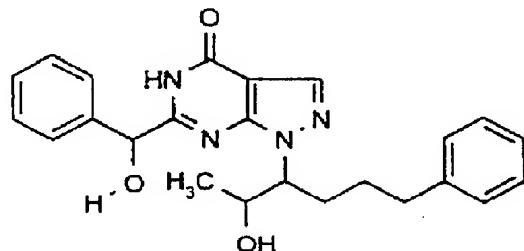
Starting from 2.1 g (6.95 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazole-4-carboxamide and 4.05 mg (17.38 mmol) of 4-bromophenylacetyl chloride, the title compounds are prepared analogously to the protocol of Example 13. This gives 594 mg (18%) of the diastereomer which elutes more rapidly, M.p.: 117°C, and 372 mg (11%) of the diastereomer which elutes more slowly, M.p.: 116°C.

15

Example 31

1-[1-(1-Hydroxy-ethyl)-4-phenyl-butyl]-6-(hydroxy-phenyl-methyl)-1,5-dihydro-pyrazolo-[3,4-*d*]pyrimidin-4-one

20



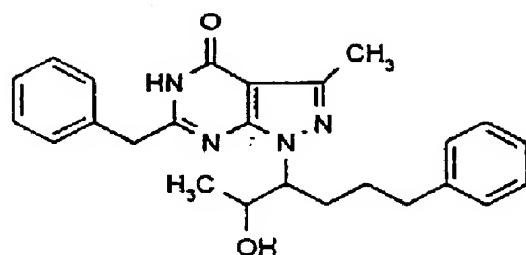
Starting from 1.25 g (4.14 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazole-4-carboxamide and 2.20 mg (10.38 mmol) of D,L-acetylmandelyl-chloride gives the title compound in a yield of 72 mg (4.2%). $R_f = 0.10$ (cyclohexane/ethyl acetate = 2:1).

5

Example 32 and Example 33

6-Benzyl-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

10



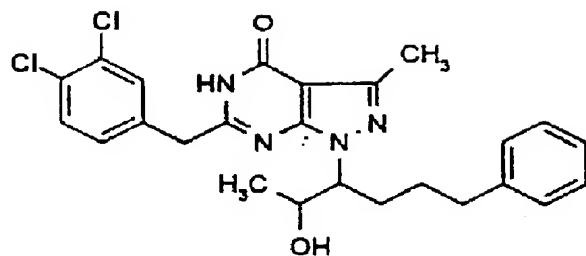
15 805 mg (2.55 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1*H*-pyrazole-4-carboxamide and 140 mg of 4-dimethylaminopyridine are dissolved in 20 ml of pyridine, and a solution of 991 mg (6.48 mmol) of phenylacetal chloride in 1 ml of toluene is added. The mixture is stirred for 3 hours at 50°C, the solvent is removed in vacuo, and the residue is taken up in 100 ml of CH_2Cl_2 . The mixture is extracted with 1N HCl, saturated in NaHCO_3 solution and water, the extract is dried over Na_2SO_4 , and the solvent is removed in vacuo.

20

25 The reaction product is dissolved in 45 ml of ethanol, 8 ml of water and 2.0 g of NaOH are added, and the mixture is refluxed for 3 hours. The solvents are removed in vacuo, 1N HCl is added and the mixture is then extracted twice with EtOAc, the extract is dried over Na_2SO_4 and the solvent is removed in vacuo. Purification by chromatography (PE/EA = 2:1) gives 216 mg (20%) of a diastereomer with elutes more rapidly, $R_f = 0.2$ (cyclohexane/ethyl acetate = 2:1) and 156 mg (15%) of the diastereomer which elutes more slowly, $R_f = 0.1$ (cyclohexane/ethyl acetate = 2:1).

30

Example 34 and Example 35
6-(3,4-Dichloro-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



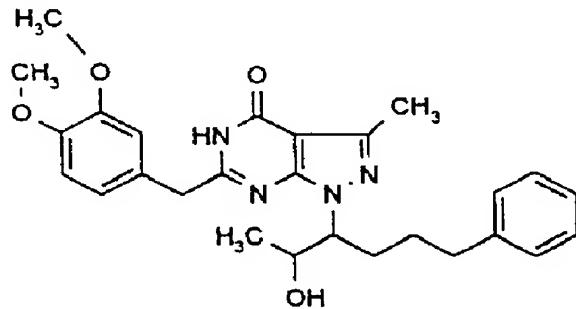
Starting from 805 mg (2.55 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenylbutyl]-3-methyl-1*H*-pyrazole-4-carboxamide and 1.41 g (6.59 mmol) of 3,4-dichlorophenylacetyl chloride, are employed analogously to the protocol of Example 32 and 33. This gives 217 mg (18%) of the diastereomer which elutes more rapidly, $R_f = 0.2$ (cyclohexane/ethyl acetate = 2:1) and 186 mg (15%) of the diastereomer which elutes more slowly, M.p.: 160°C.

10

Example 36

6-(3,4-Dimethoxy-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

15



The title compound is obtained starting from 805 mg (2.55 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenylbutyl]-3-methyl-1*H*-pyrazole-4-carboxamide and 1.37 g (6.40 mmol) of 3,4-dimethoxyphenyl acetyl chloride.

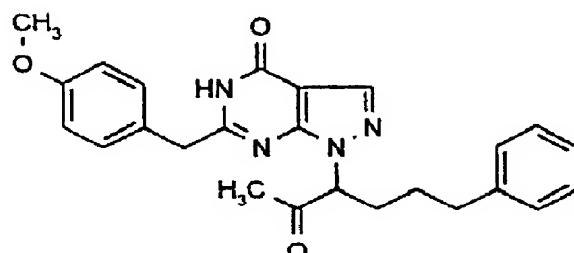
Yield: 139 mg (9%)

$R_f = 0.1$ (cyclohexane/ethyl acetate = 2:1).

Example 37

1-(1-Acetyl-4-phenyl-butyl)-6-(4-methoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

5



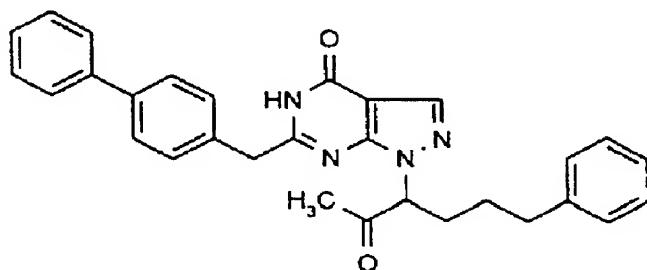
151 mg (0.35 mmol) of 1-[1-(-hydroxy-ethyl)-4-phenyl-butyl]-6-(4-methoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one are dissolved in 1 ml of DMSO and 3.5 ml of dichloromethane, and the solution is cooled to 0°C. 0.485 ml of triethylamine and 245 mg of SO₃/pyridine complex are added, and the mixture is stirred for 15 hours at room temperature. The mixture is diluted with 20 ml of dichloromethane, extracted with 1N HCl and saturated NaHCO₃ solution, the extract is dried over Na₂SO₄, and the solvent is removed in vacuo. Purification by chromatography (PE-EA = 2:1) gives 115 mg (76%), M.p.: 129°C.

10

Example 38

1-(1-Acetyl-4-phenyl-butyl)-6-biphenyl-4-ylmethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

20



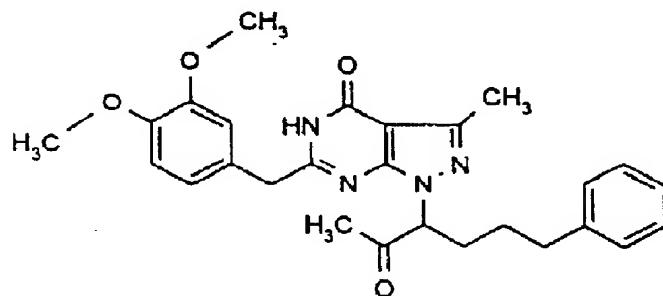
25

The title compound is obtained starting from 299 mg (0.62 mmol) of 6-biphenyl-4-ylmethyl-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1,5-dihydro-pyrazolo[3,4-*d*]-pyrimidin-4-one in a yield of 268 mg (91%).
M.p.: 107°C.

Example 39

1-(1-Acetyl-4-phenyl-butyl)-6-(3,4-dimethoxy-benzyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

5

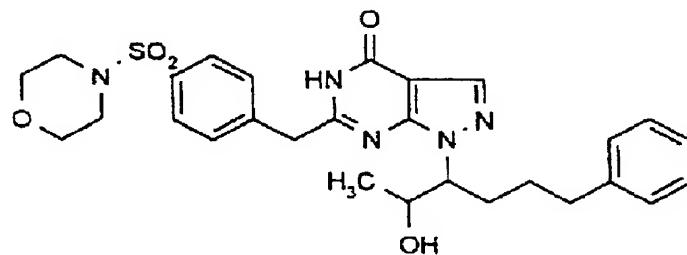


The title compound is obtained starting from 237 mg (0.51 mmol) of 6-(3,4-dimethoxy-benzyl-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]-pyrimidin-4-one in a yield of 165 mg (70%).
10 M.p.: 120°C.

Example 40

15

6-[4-Morpholine-4-sulphonyl]-benzyl][1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



20

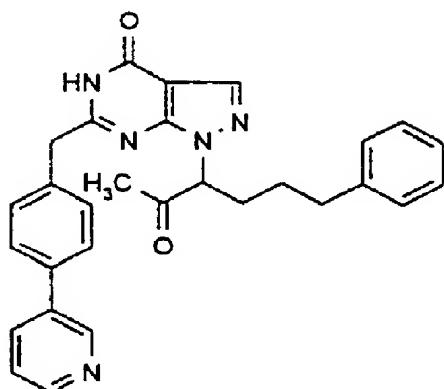
785 mg (2.48 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1*H*-pyrazole-4-carboxamide, 1.40 g of potassium *tert*-butoxide and 1.67 g (5.58 mmol) of methyl 4-(morpholinosulphonyl)-phenylacetate are refluxed overnight in 18 ml of ethanol. The solvent is removed in vacuo, taken up in dichloromethane, extracted with 1N HCl, and the organic phase is dried over Na₂SO₄ and evaporated on a rotary evaporator. Purification by chromatography (twice;

dichloromethane/methanol = 30/1), gives 375 mg (28%). R_f = 0.33 (dichloromethane/methanol = 30/1).

Example 41

5

1-(1-Acetyl-4-phenyl-butyl)-6-(4-(3-pyridyl)-benzyl)-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



10

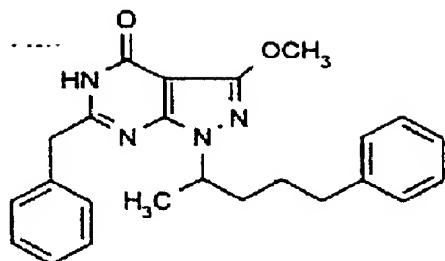
71 mg (0.48 mmol) of diethyl-(3-pyridyl)-borane and 16 mg of tetrakis(triphenylphosphine)-palladium are added under argon to a solution of 177 mg (0.37 mmol) of 1-(1-acetyl-4-phenyl-butyl)-6-(4-bromo-benzyl)-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one in 4 ml of THF, and the mixture is stirred for one hour at 70°C. After 0.522 ml of 2 N Na_2CO_3 solution have been added, the mixture is stirred for a further 4 hours at 70°C, a further 27 mg (0.185 mmol) of diethyl-(3-pyridyl)-borane and 16 mg of tetrakis(triphenylphosphine)-palladium are added, and the mixture is stirred for 14 hours under reflux. The solvent is removed in vacuo and the residue taken up in CH_2Cl_2 . The mixture is extracted with 2N HCl, and the aqueous phase is rendered alkaline with 1N NaOH and extracted twice with CH_2Cl_2 . After the mixture has been dried over Na_2SO_4 , the solvent is removed in vacuo. Purification by chromatography (toluene/ethyl acetate = 4:1) gives 110 mg (6.4%) of a pale yellow solid.

M.p.: 108°C.

25

Example 42

6-Benzyl-3-methoxypyrazolo[3,4-*d*]pyrimidin-4(5H)-one



4.6 g of 5-Amino-4-cyano-3-methoxy-1-[(5-phenyl)-pent-2-yl]-pyrazole are dissolved in 25 ml of pyridine. 2.2 ml of phenylacetyl chloride are slowly added dropwise at approx. 0°C. The reaction mixture is stirred overnight at approx. 20°C. Then, a further 0.7 ml of phenylacetyl chloride are added, and stirring is continued for 2 hours. For work-up, the mixture is diluted with ethyl acetate and extracted twice with dilute citric acid solution. The ethyl acetate phase is dried with magnesium sulphate and evaporated in vacuo. This gives 7.5 g of a brown oil which is then heated at 100°C in a mixture of 75 ml of 1N sodium hydroxide solution and 4.5 ml 35% strength hydrogen peroxide. For work-up, ice is added and the mixture is extracted twice with ethyl acetate. The combined ethyl acetate phases are washed with dilute thiosulphate solution and with dilute citric acid solution, dried with magnesium sulphate and evaporated in vacuo. This gives 5.1 g of a yellow oil which is chromatographed on silica gel (Merck Si 60 0.04-0.063 mm) with a cyclohexane/ethyl acetate mixture in a ratio of 100:0 to 1:1. 5 fractions are obtained:

Fraction 1: 0.46 g of 4-cyano-3-methoxy-5-(phenylacetyl)amino-1-[5-phenyl-pent-2-yl]-pyrazole

Fraction 2: 0.08 g of 5-amino-4-cyano-3-methoxy-1-[(5-phenyl)-pent-2-yl]-pyrazole

Fraction 3: 2.0 g of 6-benzyl-3-methoxy-1-[5-phenyl-pent-2-yl]pyrazolo[3,4-d]-pyrimidin-4(5H)-one, contaminated with 5-amino-4-cyano-3-methoxy-1-[5-phenyl-pent-2-yl]-pyrazole

Fraction 4: 0.9 g of 6-benzyl-3-methoxy-1-[5-phenyl-pent-2-yl]pyrazolo[3,4-d]-pyrimidin-4(5H)-one

Fraction 5: 0.5 g of 5-amino-4-carboxamido-3-methoxy-1-[5-phenyl-pent-2-yl]-pyrazole

NMR of 6-benzyl-3-methoxy-1-[5-phenyl-pent-2-yl]-pyrazolo[3,4-d]pyrimidin-4(5H)-one (fraction 4)

(300 MHZ, CD₃OD) 1.2-1.5[2]m; 1.4[3]d J=8 Hz; 1.6-1.75[1]m; 1.9-2.05[1]m; 2,-2.6[2]m; 3.9[2]s; 3.95[3]s; 4.75-4.85[1]m; 7.0[2]d; 7.05-7.35[8]m

TLC of 6-benzyl-3-methoxy-1-[5-phenyl-pent-2yl]-pyrazolo[3,4-d]pyrimidin-4(5H)-one (fraction 4)

5 R_f value = 0.4; mobile phase: petroleum ether/ethyl acetate 1:1; Merck Si60 Art. No. 1.05719

NMR of 5-amino-4-carboxamido-3-methoxy-1-[5-phenyl-pent-2-yl]-pyrazole (fraction 5)

(300 MHZ, CD₃OD) 1.3[3]d J=8 Hz; 1.35-1.65[3]m 1.85-2.0[1]m; 2.5-2.65[2]m;

10 3.9[3]s; 4.1-4.2[1]m; 7.1-7.15[3]m; 7.2-7.25[2]m

TLC of 5-amino-4-carboxamido-3-methoxy-1-[5-phenyl-pent-2-yl]-pyrazole (fraction 5)

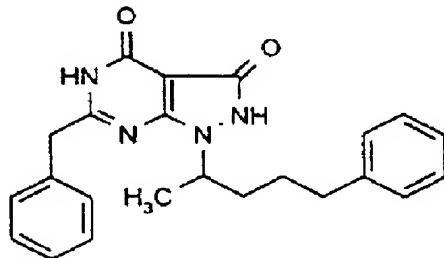
R_f value = 0.16; mobile phase: petroleum ether/ethyl acetate 1:1; Merck Si60 Art.

No. 1.05719

15

Example 43

6-Benzyl-1-[5-phenyl-pent-2yl]-pyrazolo[3,4-d]pyrimidin-3,4(2H,5H)-one



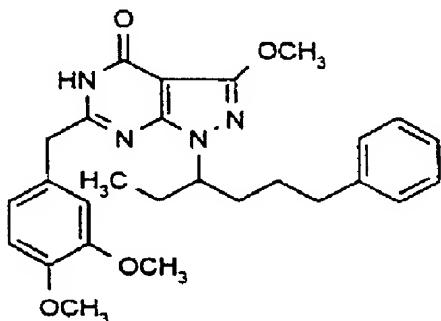
20

1.6 g of 6-Benzyl-3-methoxy-1-[5-phenyl-pent-2yl]-pyrazolo[3,4-d]pyrimidin-4(5H)-one (fraction 3 in the abovementioned example), together with 0.75 g of sodium iodide are dissolved in 25 ml of absolute acetonitrile. After 0.63 ml of trimethylchlorosilane have been added, the mixture is refluxed for 2 hours. For work-up, the reaction mixture is poured into dilute sodium thiosulphate solution and extracted with ethyl acetate. The two-phase mixture contains the product as a white crystalline precipitate. The precipitate is filtered off with suction, washed with ethyl acetate and water and dried in vacuo. This gives 0.636 g (= 61% of theory) of 6-benzyl-1-[5-phenyl-pent-2yl]-pyrazolo[3,4-d]pyrimidin-3,4(2H,5H)-one, M.p. = 275°C.

NMR of 6-benzyl-1-[5-phenyl-pent-2-yl]-pyrazolo[3,4-d]pyrimidin-3,4(2H,5H)-one (200 MHZ, DMSO-d6) 1.1-1.4[2]m; 1.3[3]d J=8 Hz; 1.55-1.9[2]m; 2.35-2.6[2]m; 3.85[2]s; 4.6-4.8[1]m; 7.0-7.4[10]m; 10.9[1]s broad; 11.9[1]s broad

5 **Example 44**

6-(3,4-Dimethoxybenzyl)-3-methoxy-1-[5-phenyl-pent-2-yl]-pyrazolo[3,4-d]pyrimidin-4(5H)-one



10

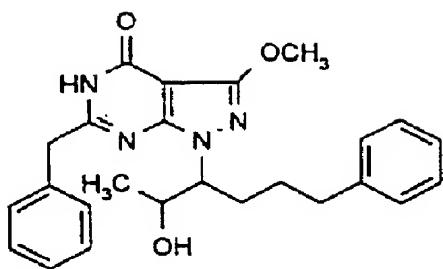
0.416 g of 5-amino-4-carboxamido-3-methoxy-1-[5-phenyl-pent-2-yl]-pyrazole together with 1.34 g of ethyl 3,4-dimethoxyphenylacetate and 1.18 g of potassium tert-butoxide is refluxed for 2 hours in 6 ml of absolute ethanol. For work-up, the mixture is diluted with ethyl acetate and washed twice with saturated sodium hydrogen carbonate solution. The ethyl acetate phase is dried with magnesium sulphate and evaporated in vacuo. The evaporation residue crystallizes from diethyl ether. After filtration with suction and drying in vacuo, 0.528 g (= 82.7% of theory) of 6-(3,4-dimethoxybenzyl)-3-methoxy-1-[5-phenyl-pent-2-yl]-pyrazolo[3,4-d]pyrimidin-4(5H)-one is obtained as white crystals, M.p. = 148°C.

15 NMR (200 MHZ, CDCl₃) 1.45[3]d J=8 Hz; 1.35-1.55[2]m; 1.65-1.85[1]m; 1.95-2.15[1]m; 2.5-2.7[2]m; 3.8[3]s; 3.85[3]s; 3.95[2]s; 4.0[3]s; 4.75-4.90[1]m; 6.75[1]d J=8 Hz; 6.85-7.0[2]m; 7.1-7.3[5]m

20 TLC R_f value = 0.5; mobile phase: dichloromethane/methanol 10:1, Merck Si60 Art. No. 1.05719

Example 45

30 6-Benzyl-3-methoxy-1-[2-hydroxy-(6-phenyl)-hex-3-yl]-pyrazolo[3,4-d]pyrimidin-4(5H)-one

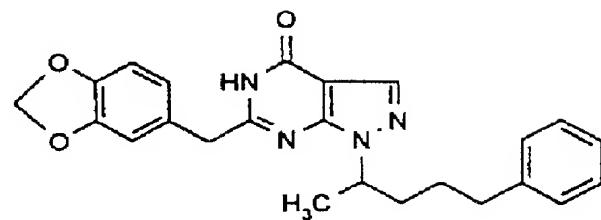


0.94 g of 5-amino-4-cyano-3-methoxy-1-[2-hydroxy-6-phenyl-hex-3-yl]-pyrazole is dissolved in 5 ml of pyridine. 0.98 ml of phenylacetal chloride is slowly added dropwise at approx. 0°C. The reaction mixture is stirred overnight at approx. 20°C. Then, a further 0.25 ml of phenyl acetal chloride are added and stirring is continued for 1 hour. For work-up, the mixture is diluted with ethyl acetate and extracted twice with dilute citric acid solution. The ethyl acetate phase is dried with magnesium sulphate and evaporated in vacuo. This gives 2.16 g of a brown oil which is then heated for 6 hours at 100°C in a mixture of 15 ml of 1N sodium hydroxide solution and 0.78 ml of 35% strength hydrogen peroxide. For work-up, ice is added and the mixture is extracted twice with ethyl acetate. The combined ethyl acetate phases are washed with dilute thiosulphate solution and with dilute citric acid solution, dried with magnesium sulphate and evaporated in vacuo. This gives 2 g of an oil which is chromatographed on silica gel (Merck Si60 0.04-0.063 mm) with a cyclohexane/ethyl acetate mixture in a ratio of 50:0 to 2:1. This gives several fractions, of which one affords 0.185 g (= 15% of theory) of 6-benzyl-3-methoxy-1-[2-hydroxy-(6-phenyl)-hex-3-yl]-pyrazolo[3,4-d]pyrimidin-4(5H)-one as diastereomer mixture after evaporation.

NMR (300 MHZ, CD₃OD) 0.9 and 1.1[3]d J=8 Hz; 1.2-1.4[2]m; 1.65-1.8 and 1.95-2.1[2]m; 2.4-2.7[2]m; 3.9[3]s; 3.95[2]s; 4.0-4.1[1]m; 4.4-4.55[1]m; 6.95-7.35[10]m.

25 **Example 46**

6-(3,4-Methylenedioxy-benzyl)-1-(1-methyl-4-phenyl-butyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one

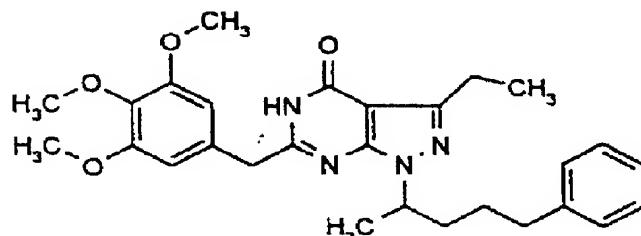


18 mg (0.066 mmol) of 5-amino-1-(1-methyl-4-phenyl-butyl)-1*H*-pyrazole-4-carboxamide and 41 mg (0.21 mmol) of methyl 3,4-methylenedioxophenylacetate are refluxed for 6 hours in 1 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 18 mg (64%) of a solid, R_f = 0.34 (dichloromethane/methanol = 15:1).

10 **Example 47**

6-(3,4,5-Trimethoxy-benzyl)-1-(1-methyl-4-phenyl-butyl)-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

15

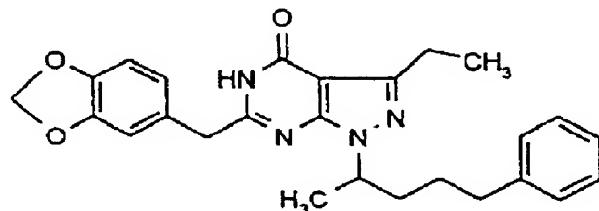


400 mg (1.4 mmol) of 5-amino-3-ethyl-1-(1-methyl-4-phenyl-butyl)-1*H*-pyrazole-4-carboxamide, 750 mg (6.7 mmol) of potassium *tert*-butoxide and 720 mg (3.0 mmol) of methyl 3,4,5-trimethoxy-phenylacetate are refluxed for 16 hours in 10 ml of ethanol. After the solvent has been removed, the mixture is acidified with 1N HCl, extracted 3 times with dichloromethane, the organic phase is dried over sodium sulphate and the solvent is removed in vacuo. Purification by chromatography gives 286 mg (40%) of a solid, R_f = 0.62 (ethyl acetate/cyclohexane = 2:1).

Example 48

6-(3,4-Methylenedioxy-benzyl)-1-(1-methyl-4-phenyl-butyl)-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

5

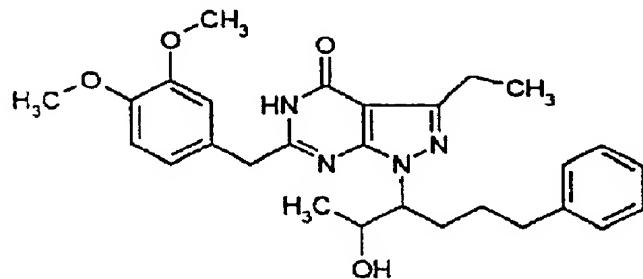


19 mg (0.063 mmol) of 5-amino-1-(1-methyl-4-phenyl-butyl)-3-ethyl-1*H*-pyrazole-4-carboxamide and 35 mg (0.180 mmol) of methyl 3,4-methylenedioxyphenylacetate are refluxed for 6 hours in 0.9 ml of 0.5M ethanolic potassium *tert*-butoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 14 mg (48%) of a solid, $R_f = 0.64$ (dichloromethane/methanol = 15:1).

15 **Examples 49 and 50**

6-(3,4-Dimethoxy-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

20



1.0 g (3.03 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-ethyl-1*H*-pyrazole-4-carboxamide, 1.60 g of potassium *tert*-butoxide and 1.40 g (19 mmol) of methyl 3,4-dimethoxyphenylacetate are refluxed overnight in 20 ml of ethanol. The solvent is removed in vacuo, the residue is taken up in dichloromethane, the mixture is extracted with 1N HCl, the organic phase is dried over Na_2SO_4 and evaporated on a rotary evaporator. Purification by chromatography (cyclohexane/EA = 2:1, 1%

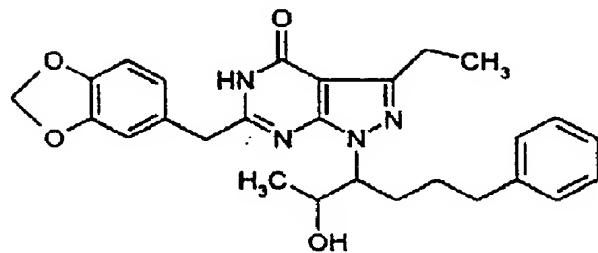
formic acid) and separation of the diastereomers by chromatography gives 232 mg (16%) of the diastereomer which elutes more rapidly, $R_f = 0.2$ (cyclohexane/ethyl acetate = 2:1) and 150 mg (10%) of the diastereomer which elutes more slowly, $R_f = 0.15$ (cyclohexane/ethyl acetate = 2:1).

5

Example 51

6-(3,4-methylenedioxy-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

10



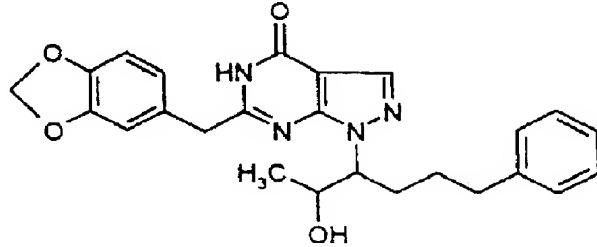
15 10 mg (0.037 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-ethyl-1*H*-pyrazole-4-carboxamide and 30 mg (0.129 mmol) of methyl 3,4-methylenedioxypheyl acetate are refluxed for 6 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 3 mg (20%) of a solid, $R_f = 0.65$ (dichloromethane/methanol = 15:1).

20

Example 52

6-(3,4-Methylenedioxy-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

25

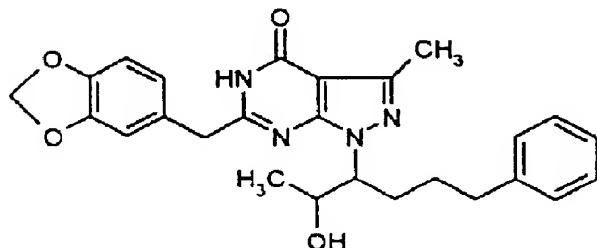


20 mg (0.066 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-1*H*-pyrazole-4-carboxamide and 41 mg (0.210 mmol) of methyl 3,4-methylenedioxyphenylacetate are refluxed for 6 hours in 1.06 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After dichloromethane and saturated 5 aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 19 mg (64%) of a solid, R_f = 0.20 (dichloromethane/methanol = 15:1).

Example 53

10

6-(3-,4-Methylenedioxy-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



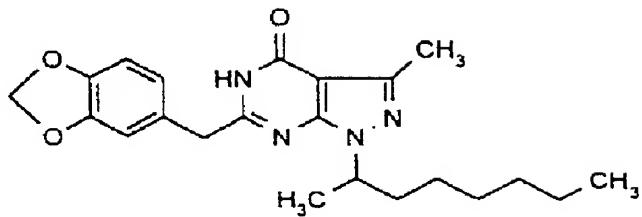
15

10 mg (0.037 mmol) of 5-amino-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1*H*-pyrazole-4-carboxamide and 30 mg (0.129 mmol) of methyl 3,4-methylenedioxyphenylacetate are refluxed for 6 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After dichloromethane and saturated 20 aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 5 mg (31%) of a solid, R_f = 0.44 (dichloromethane/methanol = 15:1).

Example 54

25

6-(3,4-Methylenedioxy-benzyl)-1-(2-octyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

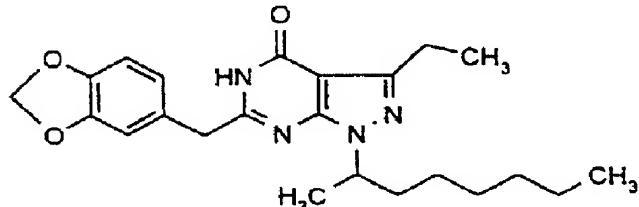


10 mg (0.037 mmol) of 5-amino-3-methyl-1-(2-octyl)-1*H*-pyrazole-4-carboxamide and 30 mg (0.129 mmol) of methyl 3,4-methylenedioxyphenylacetate are refluxed for 5 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 2 mg (16%) of a solid, $R_f = 0.67$ (dichloromethane/methanol = 15:1).

10 **Example 55**

6-(3,4-Methylenedioxy-benzyl)-1-(2-octyl)-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

15

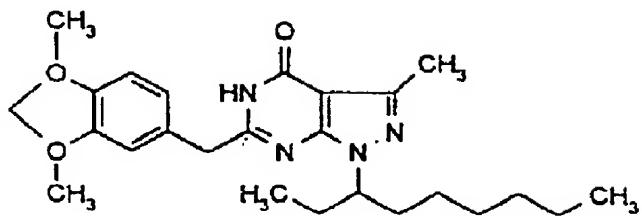


10 mg (0.037 mmol) of 5-amino-3-ethyl-1-(2-octyl)-1*H*-pyrazole-4-carboxamide and 30 mg (0.129 mmol) of methyl 3,4-methylenedioxyphenylacetate are refluxed for 6 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After 20 dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 4 mg (25%) of a solid, $R_f = 0.76$ (dichloromethane/methanol = 15:1).

Example 56

25

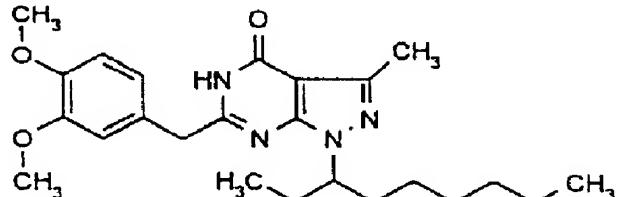
6-(3,4-Methylenedioxy-benzyl)-1-(3-nonyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



15 mg (0.055 mmol) of 5-amino-3-methyl-1-(3-nonyl)-1*H*-pyrazole-4-carboxamide and 53 mg (0.274 mmol) of methyl 3,4-methylenedioxophenylacetate are refluxed for 5 6 hours in 0.5 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 11.8 mg (52%) of a solid, $R_f = 0.65$ (dichloromethane/methanol = 15:1).

10 **Example 57**

6-(3,4-Dimethoxy-benzyl)-1-(3-nonyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



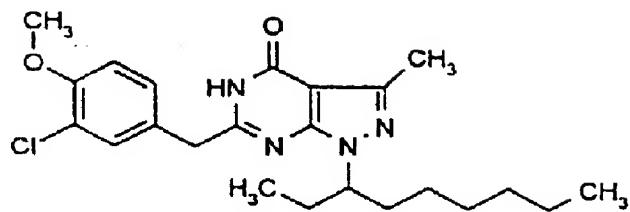
15

10 mg (0.036 mmol) of 5-amino-3-methyl-1-(3-nonyl)-1*H*-pyrazole-4-carboxamide and 57 mg (0.274 mmol) of methyl 3,4-dimethoxyphenylacetate are refluxed for 6 hours in 0.5 ml of a 0.5M ethanolic sodium ethoxide solution. After 20 dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 7.3 mg (48%) of a solid, $R_f = 0.57$ (dichloromethane/methanol = 15:1).

Example 58

25

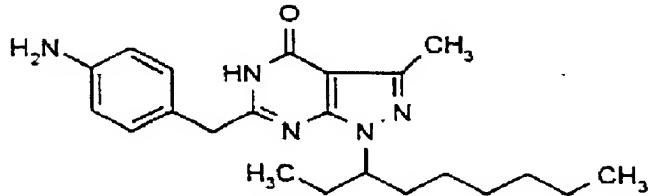
6-(3-Chloro-4-methoxy-benzyl)-1-(3-nonyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



13 mg (0.050 mmol) of 5-amino-3-methyl-1-(3-nonyl)-1*H*-pyrazole-4-carboxamide and 53 mg (0.248 mmol) of methyl 3-chloro-4-methoxyphenylacetate are refluxed for 6 hours in 0.5 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 10 mg (47%) of a solid, $R_f = 0.265$ (dichloromethane/methanol = 15:1).

10 **Example 59**

6-(4-Amino-benzyl)-1-(3-nonyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

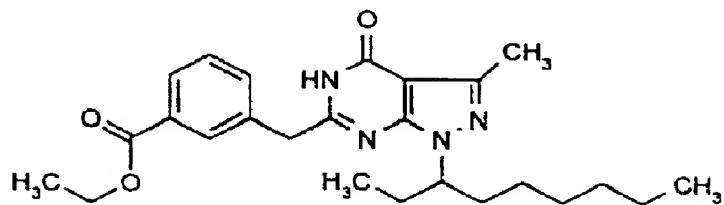


15

10 mg (0.037 mmol) of 5-amino-3-methyl-1-(3-nonyl)-1*H*-pyrazole-4-carboxamide and 45 mg (0.274 mmol) of methyl 4-aminophenylacetate are refluxed for 6 hours in 0.5 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 4.9 mg (35%) of a solid, $R_f = 0.45$ (dichloromethane/methanol = 15:1).

25 **Example 60**

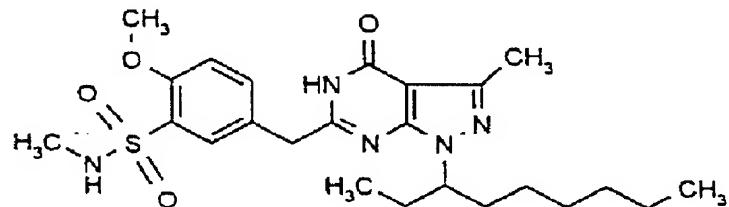
6-(3-ethoxycarbonyl-benzyl)-1-(3-nonyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



11 mg (0.042 mmol) of 5-amino-3-methyl-1-(3-nonyl)-1*H*-pyrazole-4-carboxamide and 37 mg (0.167 mmol) of methyl 3-ethoxycarbonylphenylacetate are refluxed for 5 6 hours in 0.5 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 6.8 mg (37%) of a solid, $R_f = 0.47$ (dichloromethane/methanol = 15:1).

10 **Example 61**

6-(3-N-methylaminosulphonyl-benzyl)-1-(3-nonyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



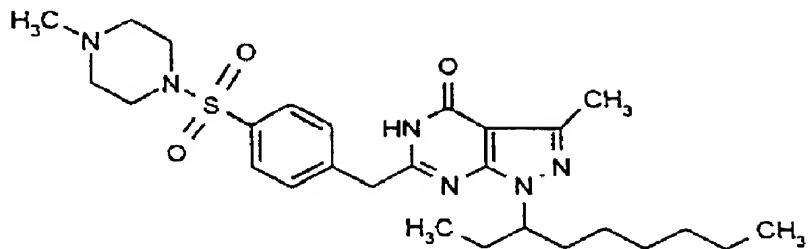
15

13 mg (0.050 mmol) of 5-amino-3-methyl-1-(3-nonyl)-1*H*-pyrazole-4-carboxamide and 46 mg (0.167 mmol) of methyl 3-N-methylaminosulphonyl-4-methoxyphenyl acetate are refluxed for 6 hours in 0.5 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 3.8 mg (16%) of a solid, $R_f = 0.36$ (dichloromethane/methanol = 15:1).

Example 62

25

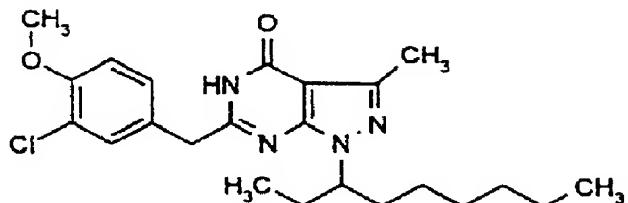
6-(4-N-methylpiperazinosulphonyl-benzyl)-1-(3-nonyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



18 mg (0.068 mmol) of 5-amino-3-methyl-1-(3-nonyl)-1*H*-pyrazole-4-carboxamide and 86 mg (0.274 mmol) of methyl 4-N-methylpiperazinosulphonylphenyl acetate are 5 refluxed for 6 hours in 0.5 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 17 mg (47%) of a solid, $R_f = 0.13$ (dichloromethane/methanol = 15:1).

10 **Example 63**

6-(3-chloro-4-methoxy-benzyl)-1-(3-nonyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



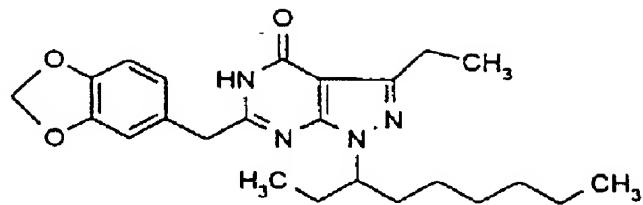
15

13 mg (0.050 mmol) of 5-amino-3-methyl-1-(3-nonyl)-1*H*-pyrazole-4-carboxamide and 53 mg (0.248 mmol) of methyl 3-chloro-4-methoxyphenylacetate are refluxed for 6 hours in 0.5 ml of a 0.5M ethanolic sodium ethoxide solution. After 20 dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 10.1 mg (47%) of a solid, $R_f = 0.63$ (dichloromethane/methanol = 15:1).

Example 64

25

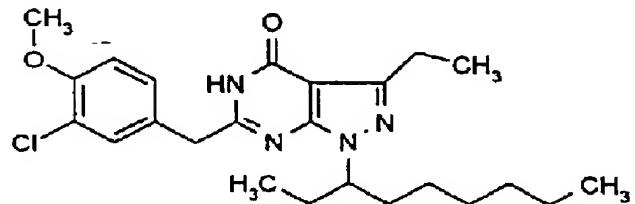
6-(3,4-methylenedioxy-benzyl)-1-(3-nonyl)-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



10 mg (0.037 mmol) of 5-amino-3-ethyl-1-(3-nonyl)-1*H*-pyrazole-4-carboxamide and 30 mg (0.129 mmol) of methyl 3,4-methylenedioxophenylacetate are refluxed for 5 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 2 mg (11%) of a solid, $R_f = 0.76$ (dichloromethane/methanol = 15:1).

10 **Example 65**

6-(3-chloro-4-methoxy-benzyl)-1-(3-nonyl)-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



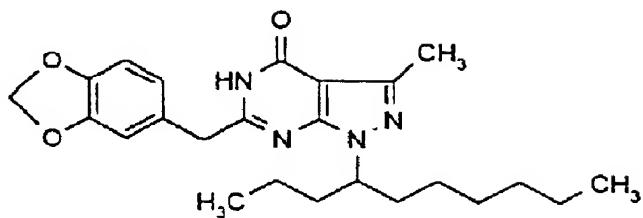
15

18 mg (0.065 mmol) of 5-amino-3-ethyl-1-(3-nonyl)-1*H*-pyrazole-4-carboxamide and 69 mg (0.323 mmol) of methyl 3-chloro-4-methoxyphenylacetate are refluxed for 6 hours in 0.5 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 8 mg (28%) of a solid, $R_f = 0.75$ (dichloromethane/methanol = 15:1).

Example 66

25

6-(3,4-Methylenedioxo-benzyl)-1-(4-decy)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

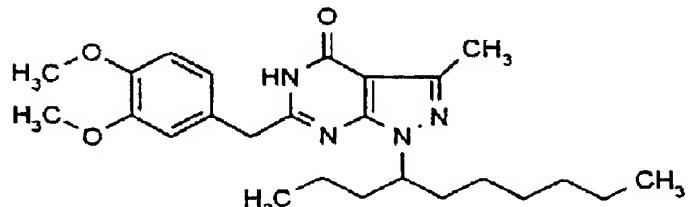


6 mg (0.021 mmol) of 5-amino-3-methyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and 20 mg (0.103 mmol) of methyl 3,4-methylenedioxophenylacetate are refluxed for 5 hours in 0.3 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 5.4 mg (59%) of a solid, $R_f = 0.60$ (dichloromethane/methanol = 15:1).

10 **Example 67**

6-(3,4-Dimethoxy-benzyl)-1-(4-decyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

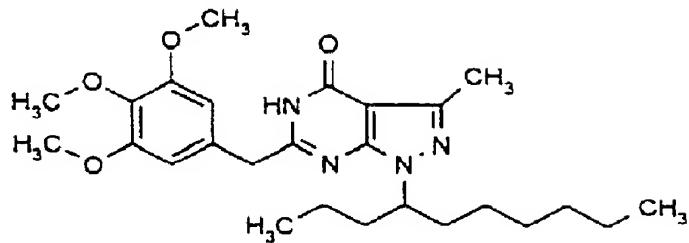
15



6 mg (0.021 mmol) of 5-amino-3-methyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and 20 mg (0.095 mmol) of methyl 3,4-dimethoxyphenylacetate are refluxed for 6 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After 20 dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 2.4 mg (26%) of a solid, $R_f = 0.66$ (dichloromethane/methanol = 15:1).

25

6-(3,4,5-trimethoxy-benzyl)-1-(4-decyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

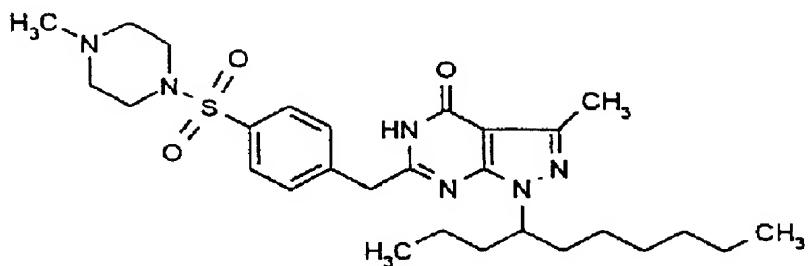


6 mg (0.021 mmol) of 5-amino-3-methyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and 20 mg (0.083 mmol) of methyl 3,4,5-trimethoxyphenylacetate are refluxed for 5 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 2.9 mg (29%) of a solid, $R_f = 0.50$ (dichloromethane/methanol = 15:1).

10 **Example 69**

6-(4-N-methylpiperazinosulphonyl-benzyl)-1-(4-decyl)-3-methyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

15



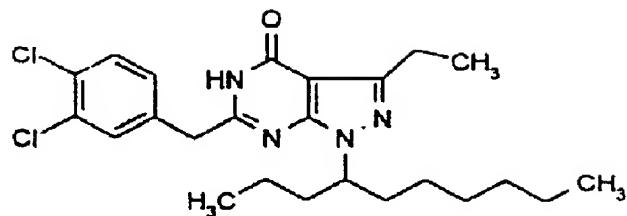
6 mg (0.021 mmol) of 5-amino-3-methyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and 20 mg (0.064 mmol) of methyl 4-N-methylpiperazinosulphonylphenyl acetate are refluxed for 6 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution.

20 After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 2 mg (17%) of a solid, $R_f = 0.45$ (dichloromethane/methanol = 15:1).

Example 70

25

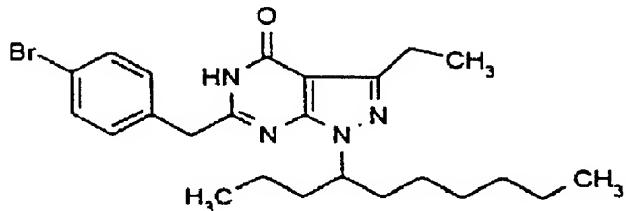
6-(3,4-Dichloro-benzyl)-1-(4-decyl)-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



10 mg (0.02 mmol) of 5-amino-3-ethyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and 20 mg (0.091 mmol) of methyl 3,4-dichlorophenylacetate are refluxed for 6 hours in 5 0.3 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 4 mg (45%) of a solid, R_f = 0.67 (dichloromethane/methanol = 15:1).

10 **Example 71**

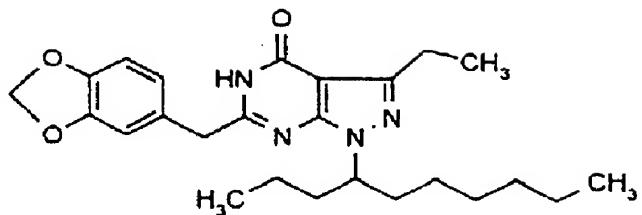
6-(4-Bromo-benzyl)-1-(4-decyl)-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



15 10 mg (0.034 mmol) of 5-amino-3-ethyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and 20 mg (0.087 mmol) of methyl 4-bromophenylacetate are refluxed for 6 hours in 0.3 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases 20 are separated. Purification by chromatography gives 7 mg (67%) of a solid, R_f = 0.69 (dichloromethane/methanol = 15:1).

Example 72

25 6-(3,4-Methylenedioxy-benzyl)-1-(4-decyl)-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

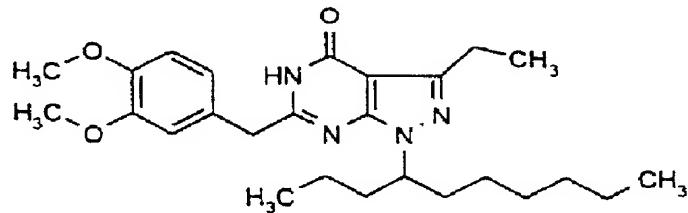


10 mg (0.034 mmol) of 5-amino-3-ethyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and 20 mg (0.103 mmol) of methyl 3,4-methylenedioxophenylacetate are refluxed for 5 6 hours in 0.3 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 4 mg (48%) of a solid, $R_f = 0.68$ (dichloromethane/methanol = 15:1).

10 **Example 73**

6-(3,4-Dimethoxy-benzyl)-1-(4-decyl)-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

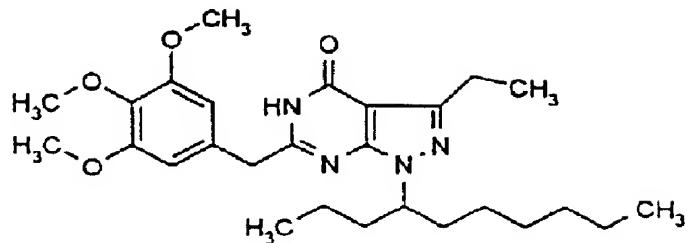
15



6 mg (0.02 mmol) of 5-amino-3-ethyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and 20 mg (0.095 mmol) of methyl 3,4-dimethoxyphenylacetate are refluxed for 6 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After 20 dichloromethane and saturated aqueous sodium hydrogen carbonate have been added, the phases are separated. Purification by chromatography gives 4 mg (42%) of a solid, $R_f = 0.47$ (dichloromethane/methanol = 15:1).

25

Example 74
6-(3,4,5-Trimethoxy-benzyl)-1-(4-decyl)-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

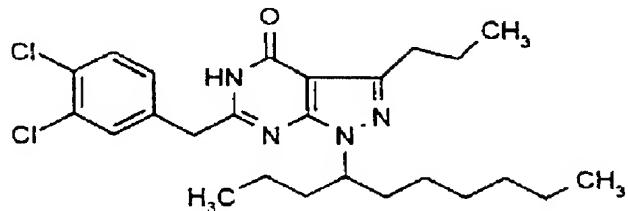


6 mg (0.02 mmol) of 5-amino-3-ethyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and 20 mg (0.083 mmol) of methyl 3,4,5-trimethoxyphenylacetate are refluxed for 5 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate have been added, the phases are separated. Purification by chromatography gives 5.5 mg (55%) of a solid, $R_f = 0.47$ (dichloromethane/methanol = 15:1).

10 **Example 75**

6-(4-N-methylpiperazinosulphonyl-benzyl)-1-(4-decyl)-3-ethyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

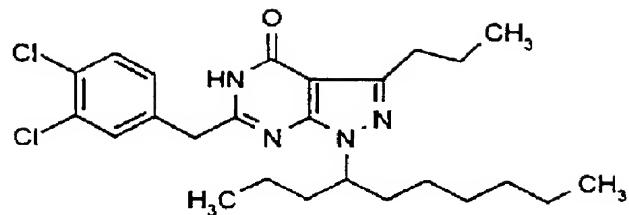
15



6 mg (0.02 mmol) of 5-amino-3-ethyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and 20 mg (0.064 mmol) of methyl 4-N-methylpiperazinosulphonylphenylacetate are refluxed for 6 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. 20 After dichloromethane and saturated aqueous sodium hydrogen carbonate have been added, the phases are separated. Purification by chromatography gives 4.3 mg (38%) of a solid, $R_f = 0.50$ (dichloromethane/methanol = 15:1).

25 **Example 76**

6-(3,4-Dichloro-benzyl)-1-(4-decyl)-3-propyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



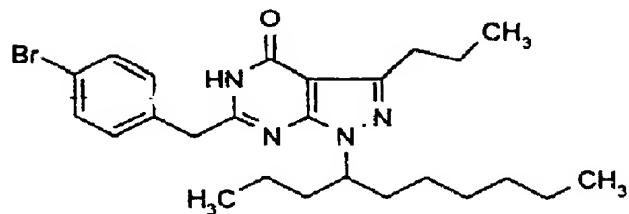
10 mg (0.019 mmol) of 5-amino-3-propyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and 20 mg (0.091 mmol) of methyl 3,4-dichlorophenylacetate are refluxed for 6 hours in 0.3 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 5 mg (48%) of a solid, $R_f = 0.70$ (dichloromethane/methanol = 15:1).

10

Example 77

15

6-(4-Bromo-benzyl)-1-(4-decyl)-3-propyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one



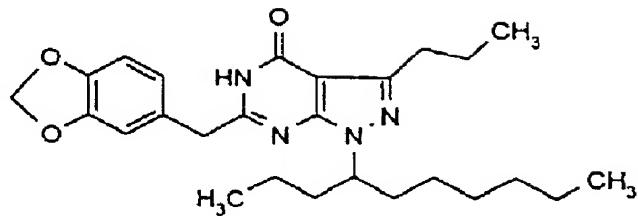
20

10 mg (0.032 mmol) of 5-amino-3-propyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and 20 mg (0.087 mmol) of methyl 4-bromophenylacetate are refluxed for 6 hours in 0.3 ml of a 0.5M ethanolic sodium ethoxide solution. After dichloromethane and saturated aqueous sodium hydrogen carbonate solution have been added, the phases are separated. Purification by chromatography gives 5 mg (53%) of a solid, $R_f = 0.69$ (dichloromethane/methanol = 15:1).

25

Example 78

6-(3,4-Methylenedioxy-benzyl)-1-(4-decyl)-3-propyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one

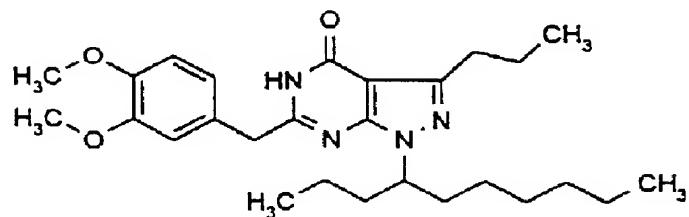


6 mg (0.019 mmol) of 5-amino-3-propyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and
5 20 mg (0.103 mmol) of methyl 3,4-methylenedioxophenylacetate are refluxed for
6 hours in 0.3 ml of a 0.5M ethanolic sodium ethoxide solution. After
dichloromethane and saturated aqueous sodium hydrogen carbonate solution have
been added, the phases are separated. Purification by chromatography gives 4.1 mg
(47%) of a solid, $R_f = 0.68$ (dichloromethane/methanol = 15:1).

10

Example 79

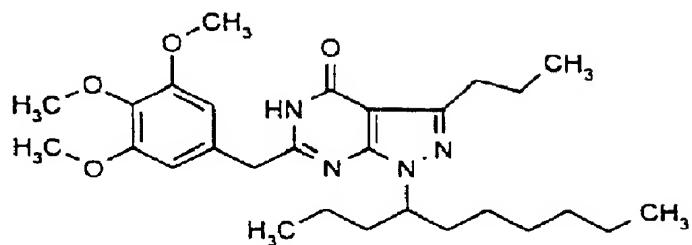
15 6-(3,4-Dimethoxy-benzyl)-1-(4-decyl)-3-propyl-1,5-dihydro-pyrazolo[3,4-
d]pyrimidin-4-one



20 6 mg (0.019 mmol) of 5-amino-3-propyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and
20 mg (0.095 mmol) of methyl 3,4-dimethoxyphenylacetate are refluxed for 6 hours
in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After
dichloromethane and saturated aqueous sodium hydrogen carbonate have been added,
the phases are separated. Purification by chromatography gives 6.6 mg (68%) of a
solid, $R_f = 0.25$ (dichloromethane/methanol = 15:1).

25 **Example 80**

25 6-(3,4,5-Trimethoxy-benzyl)-1-(4-decyl)-3-propyl-1,5-dihydro-pyrazolo[3,4-
d]pyrimidin-4-one



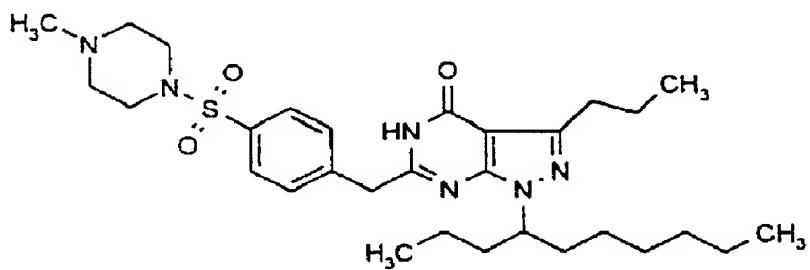
6 mg (0.019 mmol) of 5-amino-3-propyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and
 5 20 mg (0.083 mmol) of methyl 3,4,5-trimethoxyphenylacetate are refluxed for
 6 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution. After
 dichloromethane and saturated aqueous sodium hydrogen carbonate have been added,
 the phases are separated. Purification by chromatography gives 5.1 mg (56%) of a
 solid, $R_f = 0.17$ (dichloromethane/methanol = 15:1).

10

Example 81

15

6-(4-N-methylpiperazinosulphonyl-benzyl)-1-(4-decyl)-3-propyl-1,5-dihydro-
 pyrazolo-[3,4-*d*]pyrimidin-4-one

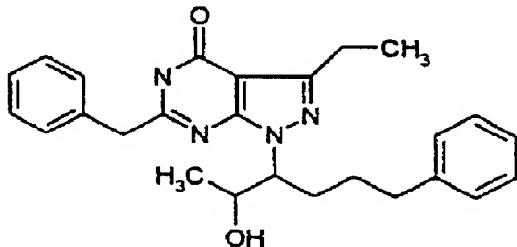


6 mg (0.019 mmol) of 5-amino-3-propyl-1-(4-decyl)-1*H*-pyrazole-4-carboxamide and
 20 mg (0.064 mmol) of methyl 4-N-methylpiperazinosulphonylphenylacetate are
 refluxed for 6 hours in 0.3 ml of a 0.5M ethanolic potassium *tert*-butoxide solution.
 After dichloromethane and saturated aqueous sodium hydrogen carbonate have been
 added, the phases are separated. Purification by chromatography gives 4 mg (36%) of
 a solid, $R_f = 0.16$ (dichloromethane/methanol = 15:1).

Examples 82 and 83

6-Benzyl-3-ethyl-1-[2-hydroxy-(6-phenyl)-hex-3-yl]-pyrazolo[3,4-*d*]pyrimidin-4(5H)-one

5



6 mg (0.02 mmol) of 5-amino-4-acetamido-3-ethyl-1-[2-hydroxy-6-phenyl-hex-3-yl]-pyrazole (diastereo mixture) together with approx. 20 mg (0.08 mmol) of phenylacetyl acetate and 0.2 ml (0.1 mmol of 0.5-molar NaOEt in EtOH are refluxed for 1.5 hours under argon. 0.5 ml of dichloromethane and 0.5 ml of 10% strength sodium hydrogen carbonate solution are added to the batch, which is stirred vigorously. The organic phase is separated off and purified by chromatography on silica gel. This gives two fractions:

10 0.5 mg (= 5.8% of theory) of a more unpolar diastereomer of 6-benzyl-3-ethyl-1-[2-hydroxy-(6-phenyl)-hex-3-yl]-pyrazolo[3,4-d]pyrimidin-4(5H)-one (TLC R_f -value = 0.75; mobile phase: dichloromethane/methanol 10:1; Merck Si60 Art No. 1.05719) and

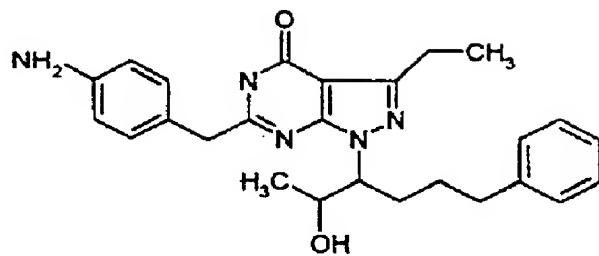
15 0.3 mg (= 3.5% of theory) of a more polar diastereomer of 6-benzyl-3-ethyl-1-[2-hydroxy-(6-phenyl)-hex-3-yl]-pyrazolo[3,4-d]pyrimidin-4(5H)-one (TLC R_f -value = 0.57; mobile phase: dichloromethane/methanol 10:1; Merck Si60 Art No. 1.05719)

20

Example 84

25

6-(4-Aminobenzyl)-3-ethyl-1-[2-hydroxy-(6-phenyl)-hex-3-yl]pyrazolo[3,4-*d*]pyrimidin-4(5H)-one

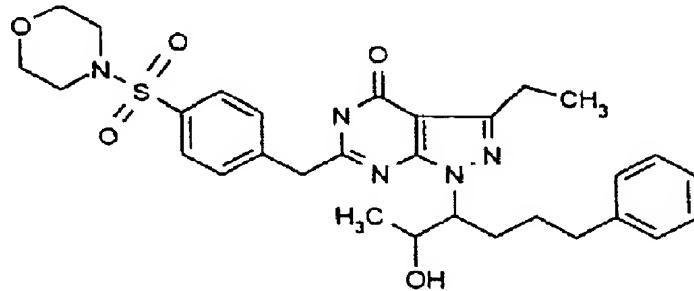


6 mg (0.02 mmol) of 5-amino-4-acetamido-3-ethyl-1-[2-hydroxy-6-phenyl-hex-3-yl]-pyrazole (diastereomer mixture) together with approx. 20 mg (0.08 mmol) of 4-aminophenylacetyl acetate and 0.2 ml (0.1 mmol) of 0.5-molar NaOEt in EtOH are refluxed for 1.5 hours under argon. 0.5 ml of dichloromethane and 0.5 ml of 10% strength sodium hydrogen carbonate solution are added to the batch, which is stirred vigorously. The organic phase is separated off and purified by chromatography on silica gel. This gives a pure fraction:

5 1.6 mg (= 18% of theory) of 6-(4-aminobenzyl)-3-ethyl-1-[2-hydroxy-(6-phenyl)-hex-3-yl]-pyrazolo[3,4-d]pyrimidin-4(5H)-one (diastereomer mixture)
(TLC R_f - value = 0.49; mobile phase: dichloromethane/methanol 10:1; Merck Si60 Art. No. 1.05719).

10 15 **Example 85**

6-(4-Morpholinosulphonylbenzyl)-3-ethyl-1-[2-hydroxy-(6-phenyl)-hex-3-yl]-pyrazolo[3,4-d]pyrimidin-4(5H)-one



20

6 mg (0.02 mmol) of 5-amino-4-acetamido-3-ethyl-1-[2-hydroxy-6-phenyl-hex-3-yl]-pyrazole (diastereomer mixture) together with approx. 20 mg (0.08 mmol) of 4-morpholinosulphonylphenylacetyl acetate and 0.2 ml (0.1 mmol) of 0.5-molar NaOEt in EtOH are refluxed for 1.5 hours under argon. 0.5 ml of dichloromethane

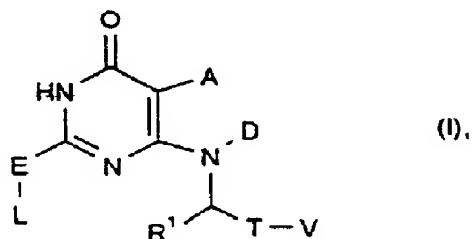
and 0.5 ml of 10% strength sodium hydrogen carbonate solution are added to the batch, which is stirred vigorously. The organic phase is separated off and purified by chromatography on silica gel. This gives a pure fraction:

2.0 mg (= 18% of theory) of 6-(4-morpholinosulphonylbenzyl)-3-ethyl-1-[2-hydroxy-
5 (6-phenyl)-hex-3-yl]-pyrazolo[3,4-*d*]pyrimidin-4(5H)one (diastereomer mixture)
(TLC R_f - value = 0.61; mobile phase: dichloromethane/methanol 10:1; Merck Si60
Art. No. 1.05719).

Patent Claims

1. 1,5-Dihydro-pyrazolo[3,4-b]-pyrimidinone derivatives of the general formula (I)

5



in which

10 A and D together represent a radical of the formula



where

15 R² represents aryl which has 6 to 10 carbon atoms and which is optionally up to trisubstituted by identical or different substituents from the series consisting of nitro, cyano, hydroxyl, trifluoromethyl, halogen, carboxyl, or by straight-chain or branched acyl, alkoxy or alkoxy carbonyl, each of which has up to 6 carbon atoms or

20 hydrogen, trifluoromethyl, cyano, carboxyl, or straight-chain or branched alkoxy or alkoxy carbonyl, each of which has up to 8 carbon atoms, or straight-chain or branched alkyl which has up to 8 carbon atoms and which is optionally substituted by hydroxyl,

25

R¹ represents straight-chain or branched acyl having up to 4 carbon atoms,
or

represents straight-chain or branched alkyl having up to 10 carbon atoms, optionally substituted by hydroxyl, azido or by a group of the formula -NR³R⁴ or -OSO₂R⁵

5

where

R³ and R⁴ are identical or different and
represent hydrogen or straight-chain or branched alkyl
having up to 6 carbon atoms, or

10

R³ and R⁴ together with the nitrogen atom form a 5 or 6-membered saturated heterocycle which can optionally contain a further hetero atom selected from the series consisting of S or O or a radical -NR⁶

15

where

R⁶ represent hydrogen or straight-chain or branched alkyl
is up to 4 carbon atoms

20

and

R⁵ represents phenyl or straight-chain or branched alkyl having up to 5 carbon atoms,

25

E represents a straight-chain or branched alkylene or alkenylene chain, each of which has up to 6 carbon atoms which are optionally substituted by hydroxyl, or
represents the C=O group,

30

L and V are identical or different and represent aryl having 6 to 10 carbon atoms or a 5- to 7-membered aromatic, optionally benzo-fused, heterocycle which has up to 3 hetero atoms from the series consisting of S, N and/or O which are optionally up to trisubstituted by identical or different substituents from the series consisting of halogen, hydroxyl, nitro, trifluoromethyl, carboxyl, straight-chain or branched

alkyl, alkoxy or alkoxy carbonyl, each of which has up to 6 carbon atoms, or by a group of the formula $-(W)_a-NR^7R^8$

where

5

a is a number 0 or 1,

W is a radical of the formula -CO or -SO₂,

10 R⁷ and R⁸ are identical or different and have the abovementioned meaning of R³ and R⁴,

15 and/or the cycles are optionally substituted by aryl having 6 to 10 carbon atoms or by a 5- to 7-membered aromatic, optionally benzofused, heterocycle having up to 3 hetero atoms from the series consisting of S, N and/or O, which, in turn, are optionally up to disubstituted by identical or different substituents from the series consisting of halogen, hydroxyl, nitro, carboxyl, trifluoromethyl or by straight-chain or branched alkyl, alkoxy or alkoxy carbonyl, each of which has up to 5 carbon atoms, or by a group of the formula
20 -(W')_b-NR⁹R¹⁰

where

25 b has the abovementioned meaning of a and is identical to this meaning or different from it,

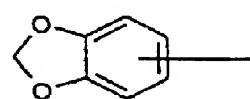
R⁹ and R¹⁰ have the abovementioned meaning of R³ and R⁴ and are identical to this meaning or different from it,

30

W' has the abovementioned meaning of W and is identical to this meaning or different from it,

or

L represents a radical of the formula



or

V represents methyl,

5 T represents a radical of the formula -CH₂-X-Y-

where

10 X represents a bond or an oxygen or sulphur atom or the -NH-group,

Y represents a straight-chain or branched alkylene chain having up to 9 carbon atoms,

15 and the tautomers and salts of these.

2. 1,5-Dihydro-pyrazolo[3,4-b]-pyrimidinone derivatives of the formula according to Claim 1

20 in which

A and D together represent a radical of the formula



or

25 where

30 R² represents phenyl which is optionally up to disubstituted by identical or different substituents from the series consisting of nitro, cyano, hydroxyl, trifluoromethyl, fluorine, chlorine, bromine, carboxyl or by straight-chain or branched acyl, alkoxy or alkoxy carbonyl, each of which has up to 5 carbon atoms, or hydrogen, trifluoromethyl, cyano, carboxyl, straight-chain or branched alkoxy or alkoxy carbonyl, each of which has up to 6

carbon atoms, or straight-chain or branched alkyl which has up to 6 carbon atoms and which is optionally substituted by hydroxyl,

5 R¹ represents straight-chain or branched acyl having up to 6 carbon atoms, or

straight-chain or branched alkyl which has up to 8 carbon atoms and which is optionally substituted by hydroxyl, azido or by a group of the formula -NR³R⁴ or O-SO₂-R⁵

10 in which

15 R³ and R⁴ are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, or

20 R³ and R⁴ together with the nitrogen atom form a morpholinyl-piperidinyl or piperazinyl ring, the latter optionally being substituted via the nitrogen function by straight-chain or branched alkyl having up to 3 carbon atoms,

and

25 R⁵ represents phenyl or straight-chain or branched alkyl having up to 4 carbon atoms,

30 E represents a straight-chain or branched alkylene or alkenylene chain, each of which has up to 5 carbon atoms and each of which is optionally substituted by hydroxyl, or
represents the C=O group,

35 L and V are identical or different and represent phenyl, naphthyl, pyridyl, thienyl, indolyl or furyl, each of which is up to trisubstituted by identical or different substituents from the series consisting of fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, nitro, carboxyl, straight-chain or branched alkyl, alkoxy or alkoxy carbonyl, each of

which has up to 5 carbon atoms, or by a group of the formula
-(W)_aNR⁷R⁸

in which

5

a represents a number 0 or 1,

W represents a radical of the formula -CO or -SO₂,

10 R⁷ and R⁸ are identical or different and have the abovementioned meaning of R³ and R⁴,

15 and/or the cycles are optionally substituted by naphthyl, phenyl, pyridyl, indolyl, thienyl or furyl, optionally by phenyl, naphthyl, pyridyl, thienyl, furyl, pyrryl or pyrimidyl, which, in turn, are optionally substituted by fluorine, chlorine, bromine, hydroxyl, nitro, carboxyl, trifluoromethyl or straight-chain or branched alkyl, alkoxy or alkoxycarbonyl, each of which has up to 3 carbon atoms, or by a group of the formula -(W')_bNR⁹R¹⁰

20

in which

b has the abovementioned meaning of a and is identical to this meaning or different from it,

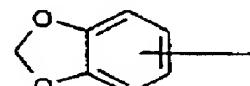
25

W' has the abovementioned meaning of W and is identical to this meaning or different from it,

30 R⁹ and R¹⁰ have the abovementioned meaning of R³ and R⁴,

or

35 L represents a radical of the formula



or

V represents methyl,

T represents a radical of the formula -CH₂-X-Y-

5 in which

X represents a bond or an oxygen or sulphur atom or the -NH-group,

10 Y represents a straight-chain or branched alkylene chain having up to 8 carbon atoms,

and the tautomers and salts of these.

15 3. 1,5-Dihydro-pyrazolo[3,4-b]-pyrimidinone derivatives of the formula (I) according to Claim 1

in which

20 A and D together represent a radical of the formula



in which

25 R² represents phenyl which is optionally up to disubstituted by identical or different substituents from the series consisting of nitro, cyano, hydroxyl, trifluoromethyl, fluorine, chlorine, bromine, carboxyl or by straight-chain or branched acyl, alkoxy or alkoxy carbonyl, each of which has up to 4 carbon atoms,

30 or

represents hydrogen, trifluoromethyl, cyano, carboxyl, straight-chain or branched alkoxy or alkoxy carbonyl, each of which has up to 5 carbon atoms, or straight-chain or branched alkyl

which has up to 5 carbon atoms and which is optionally substituted by hydroxyl,

5 R¹ represents straight-chain or branched acyl having up to 5 carbon atoms, or straight-chain or branched alkyl which has up to 6 carbon atoms and which is optionally substituted by hydroxyl, azido or by a group of the formula -NR³R⁴ or O-SO₂R⁵

10 in which

R^3 and R^4 are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, or

15 R^3 and R^4 together with the nitrogen atom form a morpholinyl, piperidinyl or piperazinyl ring, the latter optionally being methyl-substituted via the nitrogen function,

and

20

R^5 represents phenyl or straight-chain or branched alkyl having up to 3 carbon atoms,

E represents a straight-chain or branched alkylene or alkenylene chain, each of which has up to 5 carbon atoms which are optionally substituted by hydroxyl, or represents the C=O group,

L and V are identical or different and represent phenyl, naphthyl, furyl, thienyl, indolyl or pyridyl, each of which is optionally up to trisubstituted by identical or different substituents from the series consisting of fluorine, chlorine, bromine, hydroxyl, nitro, carboxyl, straight-chain or branched alkyl, alkoxy or alkoxy carbonyl, each of which has up to 4 carbon atoms, or by a group of the formula $-(W)_aNR^7R^8$

in which

a represents a number 0 or 1,

5 W represents a radical of the formula -CO or -SO₂,

R⁷ and R⁸ are identical or different and have the abovementioned meaning of R³ and R⁴,

10 and/or the cycles are optionally substituted by phenyl, pyridyl, thienyl or furyl, which, in turn, are optionally substituted by fluorine, chlorine, bromine, hydroxyl, nitro, carboxyl, trifluoromethyl or by straight-chain or branched alkyl, alkoxy or alkoxy carbonyl, each of which has up to 3 carbon atoms, or by a group of the formula -(W')_bNR⁹R¹⁰

15 in which

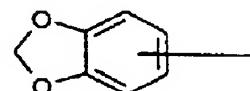
b has the abovementioned meaning of a and is identical to this meaning or different from it,

20 W' has the abovementioned meaning of W and is identical to this meaning or different from it,

25 R⁹ and R¹⁰ have the abovementioned meaning of R³ and R⁴,

or

26 L represents a radical of the formula



or

30 V represents methyl,

T represents a radical of the formula -CH₂-X-Y-

35 in which

X represents a bond or an oxygen or sulphur atom or the -NH-group,

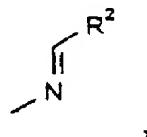
5 Y represents a straight-chain or branched alkylene chain having up to 6 carbon atoms,

and the tautomers and salts of these.

10 4. 1,5-Dihydro-pyrazolo[3,4-b]-pyrimidinone derivatives of Claims 1 to 3 as medicaments.

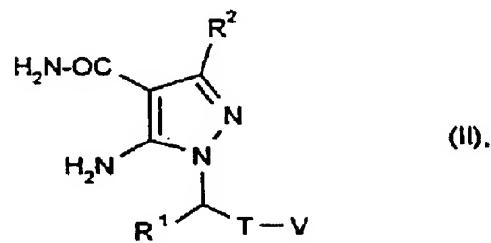
5. Process for the preparation of 1,5-dihydro-pyrazolo[3,4-b]-pyrimidinone derivatives according to Claim 1 to 3, characterized in that

15 [A] in the event that A and D together represent the radical of the formula



compounds of the general formula (II)

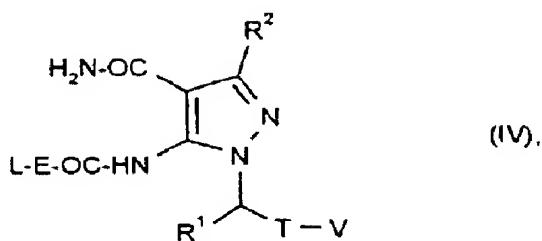
20



in which

25 R¹, R², T and V have the abovementioned meaning

are firstly converted into the compounds of the general formula (IV)



in which

5 E, L, T, V, R¹ and R² have the abovementioned meaning

by reacting them, in inert solvents and in the presence of a base, with compounds of the general formula (III)

10 L-E-CO-Cl (III)

in which

E and L have the abovementioned meaning

and subsequently cyclizing the product with bases,

or

[B] compounds of the general formula (II) are reacted, with direct cyclization, with compounds of the general formula (IIIa)

$$L-E-CO_2-R^{11} \quad (IIIa)$$

25 in which

E and L have the abovementioned meaning

and

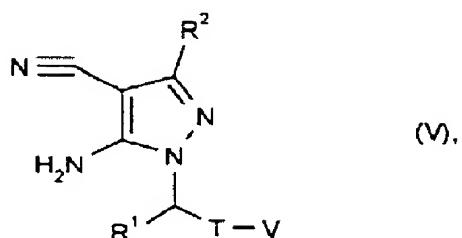
R^{11} represents methyl or ethyl,

and, in a second step, the product is cyclized in inert solvents and in the presence of a base,

or

5

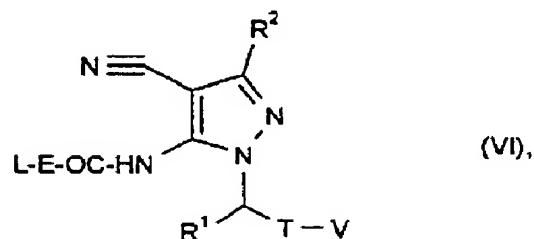
[C] compounds of the general formula (V)



10 in which

R¹, R², T and V have the abovementioned meaning

15 are first reacted with compounds of the general formula (III) in inert solvent and in the presence of a base to give the compounds of the general formula (VI)



in which

20

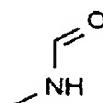
R¹, R², E, L, T and V have the abovementioned meaning,

and, in a 2nd step, cyclizing the product in inert solvents and in the presence of a base and of an oxidant,

25

or

[D] in the event that A and D together represent the radical of the formula



5 the corresponding compounds of the general formula (I) in which R² represents methoxy is reacted in the system sodium iodide/trimethylchlorosilane in inert solvents,

10 and, if appropriate, the substituents mentioned under R¹ are introduced or derivatized by subsequent reactions such as acylation, oxidation, substitution and/or reductions,

15 and, equally, the substituents mentioned above under L and V are introduced and/or varied by customary methods.

16. Medicament containing at least one 1,5-dihydro-pyrazolo[3,4-b]-pyrimidinone derivative according to Claim 1 to 3 and pharmacologically acceptable formulation auxiliaries.

20 7. Medicament according to Claim 6 for the treatment of cardiovascular and cerebrovascular diseases, diseases of the peripheral blood vessels and diseases of the urogenital tract.

25 8. Medicament according to Claim 6 and 7 for the treatment of impotence.

9. Use of 1,5-dihydro-pyrazolo[3,4-b]-pyrimidinone derivatives according to Claim 1 to 3 for the preparation of medicaments.

30 10. Use according to Claim 9 for the preparation of medicaments for the treatment of cardiovascular and cerebrovascular diseases, diseases of the peripheral blood vessels and diseases of the urogenital tract.

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